

Supporting Information for

**Total Synthesis of *N*-Methylwelwitindolinone D Isonitrile**

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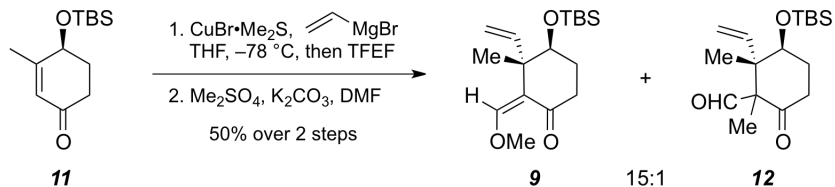
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5735 South Ellis Avenue, Chicago, IL 60637***Table of Contents**

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## General Information

Unless stated otherwise, reactions were performed in flame- or oven-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents (distilled or passed over a column of activated alumina). Commercially obtained reagents were used as received. Ambient temperature refers to 22–26 °C. Higher than ambient reaction temperatures were controlled by IKA Mag temperature modulators, while for lower temperatures ice (0 °C), MeCN/CO<sub>2</sub>(s) (–40 °C), and *i*PrOH/CO<sub>2</sub>(s) (–78 °C) baths were used. All reactions were monitored by thin-layer chromatography (TLC) which were performed using Dynamic Adsorbents pre-coated 60 Å silica gel plates (250 μm) with F-254 indicator and visualized by UV fluorescence quenching, ceric ammonium molybdate, anisaldehyde, or potassium permanganate staining. Preparative TLC was performed using Whatman Partisil PK6F pre-coated 60 Å silica gel plates (500 μm) with fluorescent indicator. Zeochem ZEOprep Flash ECO 40–63 Academic Grade silica gel (particle size 40–63 μm) was used for flash chromatography. Melting points were measured on a Fisher-Johns melting point apparatus and are uncorrected. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on Bruker DRX-500 and DMX-500 (at 500 MHz and 125 MHz, respectively) and are reported relative to Me<sub>4</sub>Si (δ 0.0), unless otherwise stated. Data for <sup>1</sup>H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Infrared spectra were recorded on a Nicolet 6700 FT-IR spectrometer and are reported in frequency of absorption (cm<sup>-1</sup>). High resolution mass spectra were recorded at Hunter College, New York, on an Agilent 6340 Ion Trap mass spectrometer.

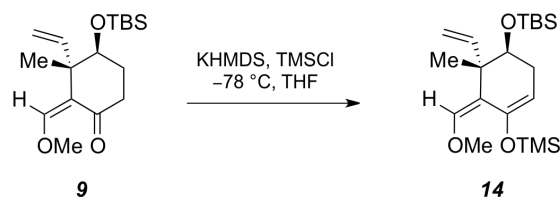
## Experimental Procedures and Characterization Data



**Vinylogous Ester 9.** A 1 L round-bottomed flask equipped with a magnetic stir bar was charged with copper(I) bromide dimethyl sulfide complex (5.10 g, 24.8 mmol, 0.8 equiv), then evacuated and backfilled with nitrogen ( $\times 3$ ). THF (170 mL) was added and the suspension was cooled to  $-78\text{ }^\circ\text{C}$ . Vinylmagnesium bromide (1.0 M in THF, 94.0 mL, 94.0 mmol, 3.0 equiv) was added dropwise over 10 min, and the resulting mixture was maintained at  $-78\text{ }^\circ\text{C}$  for an additional 30 min. A solution of enone **11** (7.50 g, 31.2 mmol, 1.0 equiv) in THF (220 mL) was then added via cannula over 30 min, and the reaction was stirred for an additional 30 min. 2,2,2-Trifluoroethylformate (TFEF; 24.2 mL, 249 mmol, 8.0 equiv) was added quickly via syringe, at which point the reaction color changed from dark red-brown to dark green. The reaction was maintained at  $-78\text{ }^\circ\text{C}$  for 5 min, after which point the cold bath was removed and the reaction was allowed to reach ambient temperature over a period of 3 h. The reaction was quenched by the addition of 0.1 N HCl (300 mL) and extracted into 1:4 EtOAc:hexanes ( $3 \times 300\text{ mL}$ ). The combined organic layers were washed with water (400 mL), brine (400 mL), dried over  $\text{MgSO}_4$ , and filtered through a 5 cm diameter plug of silica (3 cm height) on top of Celite (5 cm height) to remove residual solids. The filtrate was concentrated under reduced pressure to furnish a yellow oil. The crude vinylogous acid was carried forward without further purification.

A 500 mL round-bottom flask equipped with a magnetic stir bar was charged with  $\text{K}_2\text{CO}_3$  (12.94 g, 93.6 mmol, 3.0 equiv), then evacuated and backfilled with nitrogen ( $\times 3$ ). A solution of the crude residue from the previous reaction in DMF (160 mL) was added via syringe, followed by dimethyl sulfate (8.9 mL, 93.8 mmol, 3.0 equiv). The resulting suspension was stirred at ambient temperature for 4 h. The reaction was quenched by the addition of water (200 mL) and extracted into 1:4 EtOAc:hexanes ( $3 \times 200\text{ mL}$ ). The combined organic layers were washed with water ( $2 \times 200\text{ mL}$ ), brine (200 mL), dried over  $\text{MgSO}_4$ , and concentrated under reduced pressure. The crude residue was purified via flash chromatography (5:95  $\rightarrow$  10:90 EtOAc:hexanes) to afford an inseparable 15:1 mixture of isomeric vinylogous ester **9** and  $\beta$ -ketoaldehyde **12** (4.86 g, 50% yield) as a pale yellow oil. Data for **9**:  $R_f = 0.50$  (1:3 EtOAc:hexanes);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.43 (s, 1H), 5.71 (dd,  $J = 17.2, 10.5\text{ Hz}$ , 1H), 5.03

(dd,  $J = 10.5, 1.2$  Hz, 1H), 4.94 (dd,  $J = 17.2, 1.2$  Hz, 1H), 3.81 (s, 3H), 3.59 (app d,  $J = 3.6$  Hz, 1H), 2.57 (ddd,  $J = 18.5, 11.1, 7.2$  Hz, 1H), 2.22 (ddd,  $J = 18.5, 6.7, 3.1$  Hz, 1H), 2.04 (dddd,  $J = 13.8, 11.1, 6.7, 1.4$  Hz, 1H), 1.77 (dddd,  $J = 13.8, 7.2, 3.6, 3.1$  Hz, 1H), 1.34 (s, 3H), 0.88 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  201.0, 161.5, 143.0, 113.4, 74.0, 61.9, 47.4, 33.1, 25.9, 25.4, 22.0, -4.4, -4.9; IR (Neat film, NaCl) 2954, 2857, 1679, 1586, 1463, 1257, 1085  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calc'd for  $\text{C}_{17}\text{H}_{30}\text{O}_3\text{Si}$  [ $\text{M}^+$ ]: 310.1964, found 310.1960.



**Silyl enol ether 14.** A 50 mL round-bottomed flask equipped with a magnetic stir bar was charged with vinyllogous ester **9** (0.500 g, 1.61 mmol, 1.0 equiv) and THF (8 mL). The solution was cooled to  $-78$   $^\circ\text{C}$  and  $\text{TMSCl}$  (0.310 mL, 2.44 mmol, 1.5 equiv) was added. After 5 min,  $\text{KHMDS}$  (0.5 M in toluene, 4.85 mL, 2.43 mmol, 1.5 equiv) was added dropwise over 2 min. The reaction was stirred for 1 h, then quenched at  $-78$   $^\circ\text{C}$  by the addition of saturated aqueous  $\text{NaHCO}_3$  (10 mL). The cold bath was removed and the biphasic mixture was allowed to warm for 10 min. Water (40 mL) was added and the mixture was extracted with 1:4  $\text{EtOAc}$ :hexanes ( $3 \times 40$  mL). The combined organic layers were washed with brine (40 mL), dried over  $\text{MgSO}_4$ , and concentrated under reduced pressure to furnish a yellow oil. The crude silyl enol ether was carried forward without further purification.

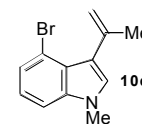


**Vinyllogous acid 8.** A 50 mL round-bottomed flask equipped with a magnetic stir bar was charged with methylmagnesium bromide (3.0 M in  $\text{Et}_2\text{O}$ , 0.810 mL, 2.43 mmol, 3.0 equiv). The flask was cooled to  $0$   $^\circ\text{C}$  and a solution of indole **13b** (0.205 g, 0.814 mmol, 1.0 equiv) in THF (8.1 mL) was added via cannula over 15 min. The reaction was maintained at  $0$   $^\circ\text{C}$  for an additional 1 h, then quenched by the

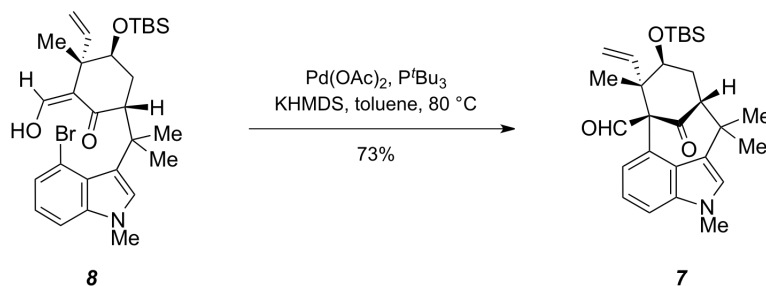
addition of ice water (20 mL). The aqueous layer was extracted with 1:4 EtOAc:hexanes (3 × 40 mL) and combined organic layers were washed with brine (40 mL), dried over MgSO<sub>4</sub>, and concentrated under reduced pressure to yield a light yellow oil. The crude tertiary alcohol (**10b**) was carried forward without further purification.<sup>1</sup>

A 50 mL round-bottomed flask equipped with a magnetic stir bar was charged with crude alcohol **10b** and THF (4 mL). The solution was cooled to -40 °C and a solution of crude silyl enol ether **14** (1.61 mmol, 2.0 equiv) in THF (4.1 mL) was added via syringe. After an additional 15 min, TMSOTf (0.145 mL, 0.801 mmol, 0.98 equiv) was added dropwise and the reaction mixture was maintained at -40 °C for 75 min. The reaction solution was then transferred via cannula to a 250 mL round-bottomed flask containing a solution of aqueous HClO<sub>4</sub> in THF (1:18 35% aq. HClO<sub>4</sub>:THF, 342 mL) at 0 °C and stirred for 10 min. The reaction was diluted with water (100 mL) and extracted into 1:4 EtOAc:hexanes (3 × 100 mL). The combined organic layers were washed with brine (100 mL), dried over MgSO<sub>4</sub>, and concentrated under reduced pressure. The crude residue was purified via flash chromatography (3:97 → 6:94 EtOAc:hexanes) to afford vinylogous acid **8** (0.349 g, 78% yield) as a white solid. *R*<sub>f</sub> = 0.54 (1:3 EtOAc:hexanes); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)<sup>2</sup> δ 8.48 (d, *J* = 4.4 Hz, 1H), 7.37 (dd, *J* = 7.6, 0.8 Hz, 1H), 7.21 (dd, *J* = 8.2, 0.8 Hz, 1H), 6.99 (app t, *J* = 7.9 Hz, 1H), 6.88 (s, 1H), 5.80 (dd, *J* = 17.3, 10.5 Hz, 1H), 5.10 (dd, *J* = 10.5, 1.0 Hz, 1H), 5.02 (dd, *J* = 17.3, 1.0 Hz, 1H), 4.20 (app t, *J* = 7.9 Hz, 1H), 3.70 (s, 3H), 3.58 (app d, *J* = 5.1 Hz, 1H), 1.87 (br s, 3H), 1.60–1.35 (comp m, 2H), 1.40 (s, 3H), 1.20 (s, 3H), 0.80 (s, 9H), -0.08 (br s, 3H), -0.26 (br s, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)<sup>2</sup> δ 192.4, 185.4, 146.4, 140.0, 128.0, 125.9, 125.5, 124.3, 122.1, 114.5, 114.0, 113.8, 108.7, 73.2, 45.4, 44.9, 38.6, 32.9, 30.4, 27.4, 26.0, 23.5, 18.1, -4.2, -4.9; IR (Neat film, NaCl) 2950, 2930, 2856, 1618, 1606, 1584, 1471, 1416, 1362, 1320, 1251, 1111, 1095, 1080 cm<sup>-1</sup>; HRMS (ESI) *m/z* calc'd for C<sub>28</sub>H<sub>40</sub>BrNO<sub>3</sub>Si [M]<sup>+</sup>: 545.1961, found 545.1958.

<sup>1</sup> Attempts to purify alcohol **10b** via flash chromatography prior to coupling with silyl enol ether **14** led to partial decomposition to form isopropene **10c**, presumably through acid-catalyzed dehydration on silica gel. As such, the alcohol was carried forward immediately following aqueous work-up.

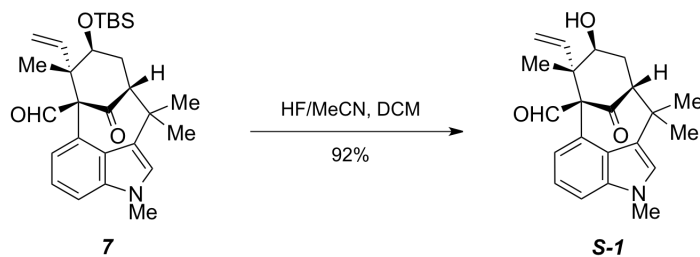


<sup>2</sup> <sup>1</sup>H and <sup>13</sup>C NMR data were acquired at 40 °C.

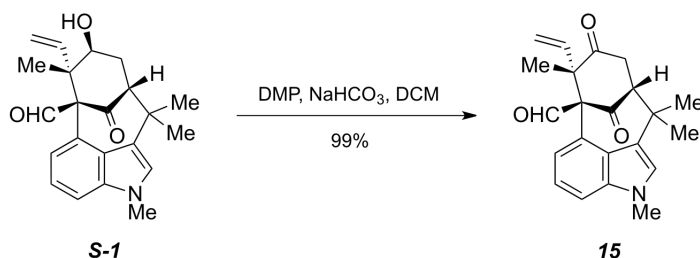


**Tetracycle 7.** A 14 mL test tube equipped with a magnetic stir bar was charged with  $\text{Pd(OAc)}_2$  (5 mg, 0.022 mmol, 0.3 equiv). Toluene (0.2 mL) was added and the flask was evacuated and backfilled with nitrogen ( $\times 3$ ). Tri-*tert*-butylphosphine (1.0 M in toluene, 0.022 mL, 0.022 mmol, 0.3 equiv) was added via syringe and the mixture was allowed to stir at ambient temperature for 5 min. KHMDS (0.5 M in toluene, 0.19 mL, 0.095 mmol, 1.3 equiv) was added dropwise via syringe, during which time the color of the solution changed from orange to dark green. After an additional 5 min, a solution of vinylogous acid **8** (40 mg, 0.073 mmol, 1.0 equiv) in toluene (4 mL) was added via syringe and the flask was evacuated and backfilled with nitrogen ( $\times 3$ ). Reaction was then placed in a preheated 80 °C oil bath. After 4.5 h, the reaction was cooled to ambient temperature and filtered over a pad of Celite. The filtrate was concentrated under reduced pressure and the crude residue was purified via preparative thin-layer chromatography (10 cm x 20 cm, 1:6 EtOAc:hexanes) to afford tetracycle **7** (25 mg, 73% yield)<sup>3</sup> as a white solid.  $R_f = 0.6$  (1:6 EtOAc:hexanes);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.84 (s, 1H), 7.32 (d,  $J = 8.0$  Hz, 1H), 7.22 (app t,  $J = 8.0$  Hz, 1H), 7.04 (s, 1H), 6.55 (d,  $J = 7.4$  Hz, 1H), 5.18–5.09 (comp m, 3H), 3.82 (s, 3H), 3.50 (dd,  $J = 11.1, 6.0$  Hz, 1H), 2.70 (d,  $J = 9.3$  Hz, 1H), 2.13 (dd,  $J = 14.4, 6.0$  Hz, 1H), 1.97 (ddd,  $J = 14.4, 11.1, 9.3$  Hz, 1H), 1.56 (s, 3H), 1.41 (s, 3H), 1.15 (s, 3H), 0.69 (s, 9H), -0.33 (s, 3H), -0.47 (s, 3H);  $^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ )  $\delta$  212.6, 197.2, 140.9, 137.5, 126.8, 126.3, 122.4, 121.7, 121.0, 115.8, 109.3, 74.2, 69.6, 60.7, 50.4, 35.7, 35.0, 33.0, 31.6, 29.7, 28.3, 25.7, 17.9, 12.9, -4.5, -5.0; IR (Neat film, NaCl) 2956, 2928, 2859, 1737, 1687, 1472, 1417, 1255, 1232, 1103  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calc'd for  $\text{C}_{28}\text{H}_{39}\text{NO}_3\text{Si}$  [ $\text{M}^+$ ]: 465.2699, found 465.2702.

<sup>3</sup> During scale-up this reaction was performed on 1.2 g of **8** with 0.25 equiv of  $\text{Pd(OAc)}_2$  and  $\text{P}^t\text{Bu}_3$  each, and provided **7** in 63% yield.

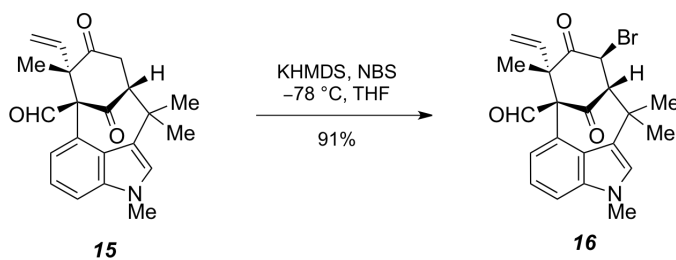


**Alcohol S-1.** A 40 mL scintillation vial equipped with a magnetic stir bar was charged with tetracycle **7** (45 mg, 0.096 mmol, 1.0 equiv) and DCM (9 mL). A solution of aqueous HF (10% v/v in MeCN, 4 mL, 22.6 mmol, 235 equiv) was added and the mixture was vigorously stirred at ambient temperature. After 12 h, a second portion of aqueous HF (1 mL, 5.7 mmol, 59 equiv) was added and the mixture was allowed to stir for an additional 3 h. The reaction was quenched by slowly pouring the reaction mixture over saturated aqueous NaHCO<sub>3</sub> (30 mL) and stirred until bubbling ceased. The biphasic mixture was extracted with DCM (3 × 30 mL) and the combined organic layers were washed with brine (50 mL), dried over MgSO<sub>4</sub>, and concentrated under reduced pressure. The crude residue was purified via flash chromatography (15:85 → 30:70 EtOAc:hexanes) to afford alcohol **S-1** (31 mg, 92% yield) as a white solid.  $R_f$  = 0.12 (1:3 EtOAc:hexanes); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 9.85 (s, 1H), 7.32 (d,  $J$  = 8.0 Hz, 1H), 7.22 (dd,  $J$  = 8.0, 7.4 Hz, 1H), 6.51 (d,  $J$  = 7.4 Hz, 1H), 5.54 (dd,  $J$  = 17.6, 11.0 Hz, 1H), 5.26 (d,  $J$  = 11.0 Hz, 1H), 5.03 (d,  $J$  = 17.6 Hz, 1H), 3.76 (s, 3H), 3.50 (dd,  $J$  = 11.5, 6.0 Hz, 1H), 2.77 (d,  $J$  = 9.6 Hz, 1H), 2.35 (dd,  $J$  = 14.4, 6.0 Hz, 1H), 1.93 (ddd,  $J$  = 14.4, 11.5, 9.6, 1H), 1.60 (s, 3H), 1.37 (s, 3H), 1.18 (s, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 212.2, 196.9, 139.6, 137.6, 127.1, 126.2, 122.2, 121.6, 121.3, 120.9, 117.5, 109.7, 74.0, 67.0, 60.4, 50.2, 35.8, 35.3, 33.0, 29.3, 28.2, 13.1; IR (Neat film, NaCl) 3444, 2965, 2952, 1732, 1686, 1450, 1418, 1367, 1335, 1232 cm<sup>-1</sup>; HRMS (ESI)  $m/z$  calc'd for C<sub>22</sub>H<sub>25</sub>NO<sub>3</sub> [M]<sup>+</sup>: 351.1834, found 351.1833.



**Dione 15.** A 1 dram vial equipped with a magnetic stir bar was charged with Dess–Martin periodinane (74 mg, 0.174 mmol, 1.5 equiv) and NaHCO<sub>3</sub> (0.032 g, 0.381 mmol, 3.3 equiv). A solution

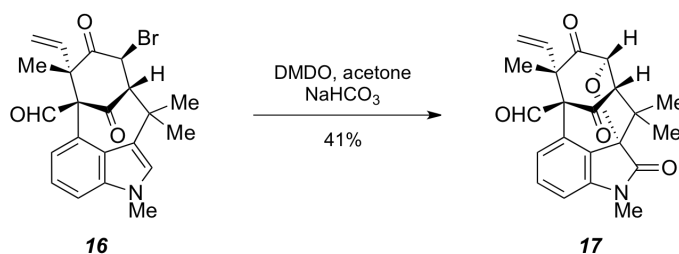
of alcohol **S-1** (40 mg, 0.114 mmol, 1.0 equiv) in DCM (1.1 mL) was added via syringe and the suspension was vigorously stirred at ambient temperature for 1.5 h. The reaction was quenched by the slow addition of saturated aqueous NaHCO<sub>3</sub> (2 mL) and the biphasic mixture was extracted with DCM (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over MgSO<sub>4</sub>, and concentrated under reduced pressure. The crude residue was purified via flash chromatography (1:3 EtOAc:hexanes) to afford dione **7** (39.4 mg, 99% yield) as a white solid. *R<sub>f</sub>* = 0.24 (1:3 EtOAc:hexanes); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 9.63 (s, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.23 (dd, *J* = 8.0, 7.4 Hz, 1H), 7.02 (s, 1H), 6.62 (d, *J* = 7.4 Hz, 1H), 5.83 (dd, *J* = 17.6, 11.0 Hz, 1H), 5.43 (d, *J* = 11.0 Hz, 1H), 5.34 (d, *J* = 17.6 Hz, 1H), 3.79 (s, 3H), 3.01 (comp m, 2H), 2.78 (m, 1H), 1.67 (s, 3H), 1.51 (s, 3H), 1.28 (s, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 209.2, 207.7, 194.7, 137.9, 135.9, 127.6, 124.4, 122.7, 121.3, 120.3, 119.6, 117.8, 110.3, 72.4, 57.9, 57.5, 39.6, 37.6, 33.1, 33.0, 28.6, 19.0; IR (Neat film, NaCl) 2967, 2924, 2854, 1736, 1715, 1690, 1458, 1418, 1333, 1215, 1150 cm<sup>-1</sup>; HRMS (ESI) *m/z* calc'd for C<sub>22</sub>H<sub>23</sub>NO<sub>3</sub> [M]<sup>+</sup>: 349.1678, found 349.1676.



**Bromodione 16.** A 50 mL round-bottomed flask equipped with a magnetic stir bar was charged with dione **15** (135 mg, 0.386 mmol, 1.0 equiv) and THF (13 mL), and cooled to  $-78$  °C. KHMDS (0.5 M in toluene, 1.00 mL, 0.5 mmol, 1.3 equiv) was added dropwise via syringe and the reaction was stirred for 20 min. A freshly prepared solution of NBS (75.6 mg, 0.425 mmol, 1.1 equiv) in THF (2 mL) was then added dropwise via syringe over 1 min and the reaction was maintained at  $-78$  °C for 1 h. The reaction was quenched at  $-78$  °C by the addition of a saturated aqueous NH<sub>4</sub>Cl (10 mL), and the cold bath was removed. The aqueous layer was extracted with 1:1 EtOAc:hexanes (3 × 40 mL) and the combined organic layers were washed with brine (50 mL), dried over MgSO<sub>4</sub>, and concentrated under reduced pressure. The crude residue was purified via flash chromatography (1:2 EtOAc:hexanes) to afford bromodione **16** (150 mg, 91% yield) as a white solid. *R<sub>f</sub>* = 0.35 (1:3 EtOAc:hexanes); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 9.63 (s, 1H), 7.32 (dd, *J* = 8.2, 0.9 Hz, 1H), 7.25 (dd, *J* = 8.2, 7.4 Hz, 1H), 7.06 (s, 1H),



6.60 (dd,  $J = 7.4, 0.9$  Hz, 1H), 5.87 (dd,  $J = 17.5, 11.1$ , Hz, 1H), 5.48 (dd,  $J = 11.1, 0.7$  Hz, 1H), 5.46 (dd,  $J = 17.5, 0.7$  Hz, 1H), 4.46 (d,  $J = 2.8$  Hz, 1H), 3.78 (s, 3H), 3.50 (dd,  $J = 2.8$  Hz, 1H), 1.97 (s, 3H), 1.71 (s, 3H), 1.25 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  206.0, 202.5, 194.0, 138.1, 135.2, 127.8, 123.7, 122.6, 121.7, 119.6, 118.7, 118.4, 110.6, 72.1, 69.3, 57.7, 43.7, 39.9, 33.1, 33.0, 28.3, 20.2; IR (Neat film, NaCl) 2973, 2925, 2853, 1738, 1727, 1702, 1462, 1417, 1372, 1333, 1214, 1150  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calc'd for  $\text{C}_{22}\text{H}_{22}\text{BrNO}_3$  [ $\text{M}^+$ ]: 427.0783, found 427.0780.

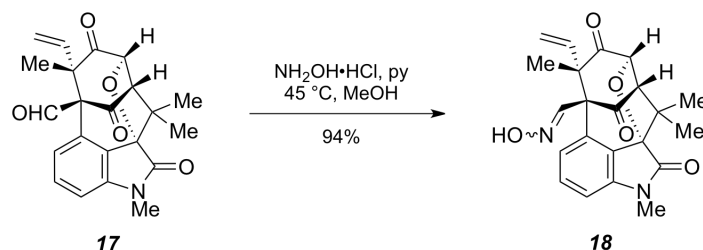


**Cyclic ether 17.** Adam's procedures were used for the preparation<sup>4</sup> and titration<sup>5</sup> of acetone solutions of DMDO (~0.1 M). DMDO solutions (3 x 2 mL) were prepared fresh each time, however, only the first batch of DMDO was titrated, the rest were used without titration. A 25 mL flask equipped with a magnetic stir bar was charged with bromodione **16** (65 mg, 0.152 mmol, 1.0 equiv),  $\text{NaHCO}_3$  (68 mg, 0.804 mmol, 5.3 equiv) and acetone (2 mL). Freshly prepared acetone solution of DMDO (2 mL, ~0.2 mmol, ~1.3 equiv) was added and the reaction was stirred at ambient temperature. The reaction was followed by TLC. After 6 h, a second portion of 2 mL DMDO was added. After an additional period of 10 h, a third portion of 2 mL DMDO was added. After a total of 24 h, the reaction was diluted with DCM (5 mL) and water (5 mL). The biphasic mixture was extracted with DCM (3 x 10 mL), washed with brine (15 mL) and dried over  $\text{MgSO}_4$ . The crude residue was purified via flash chromatography (5:6 EtOAc:hexanes) to afford cyclic ether **17** (24 mg, 41% yield) as a white solid; mp 249–252 °C. Crystals suitable for X-ray diffraction were grown via diffusion crystallization of the white solid from DCM and hexanes.  $R_f = 0.48$  (1:1 EtOAc:hexanes);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.58 (s, 1H), 7.37 (app t,  $J = 8.0$  Hz, 1H), 6.87 (d,  $J = 7.3$  Hz, 1H), 6.47 (dd,  $J = 8.0, 0.7$  Hz, 1H), 5.59 (dd,  $J = 17.1, 10.9$  Hz, 1H), 5.39 (d,  $J = 10.9$  Hz, 1H), 5.28 (d,  $J = 17.1$  Hz, 1H), 4.90 (d,  $J = 7.6$  Hz, 1H), 3.39 (d,  $J = 7.6$  Hz, 1H), 3.22 (s, 3H), 1.61 (s, 3H), 1.53 (s, 3H), 0.94 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  204.5,

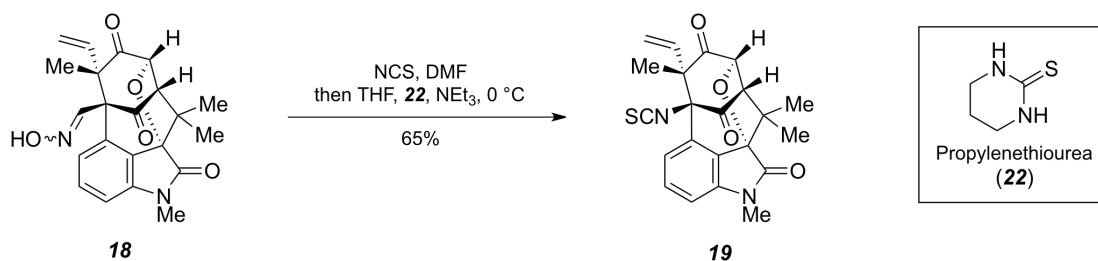
<sup>4</sup> Adam, W.; Bialas, J.; Hadjarapoglou, L. *Chem. Ber.* **1991**, *124*, 2377.

<sup>5</sup> Adam, W.; Chan, Y-Y.; Cremer, D.; Gauss, J.; Scheutzwow, D.; Schindler, M. *J. Org. Chem.* **1987**, *52*, 2800–2803.

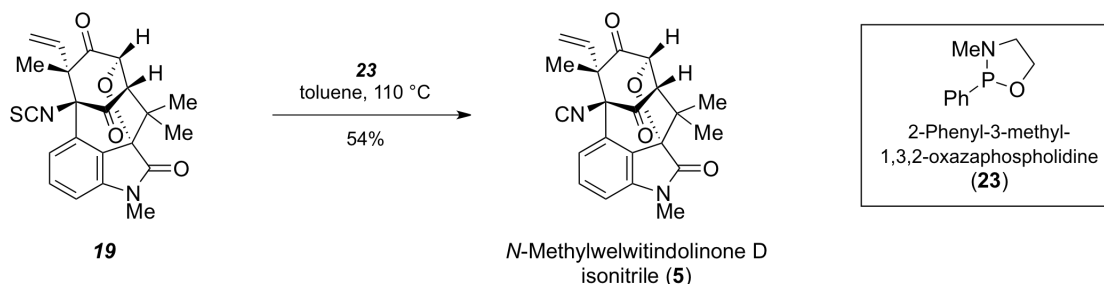
203.1, 194.2, 169.7, 145.0, 133.6, 130.7, 128.2, 126.6, 125.2, 119.7, 109.3, 85.9, 79.0, 70.2, 63.3, 59.3, 52.1, 26.7, 22.1, 19.9, 18.8; IR (Neat film, NaCl) 2975, 2933, 2855, 1724, 1698, 1608, 1588, 1463, 1367, 1345, 1202, 1051  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calc'd for  $\text{C}_{22}\text{H}_{21}\text{NO}_5$   $[\text{M}]^+$ : 379.1420, found 379.1425.



**Aldoxime 18.** A 25 mL round-bottomed flask equipped with a magnetic stir bar was charged with aldehyde **17** (33 mg, 0.087 mmol) and methanol (7 mL). Pyridine (0.035 mL, 4.33 mmol, 5.0 equiv) and hydroxylamine hydrochloride (18.1 mg, 0.26 mmol, 3.0 equiv) were added sequentially and the reaction was heated to 40  $^\circ\text{C}$ . After 15 min, the temperature was increased to 45  $^\circ\text{C}$  and the reaction was allowed to stir for 1 h 45 min. The reaction was quenched by the addition of 1.0 N HCl (2 mL) and extracted into EtOAc ( $3 \times 10$  mL). The combined organic layers were dried over  $\text{MgSO}_4$ , filtered, and concentrated under reduced pressure. The crude residue was purified via flash chromatography (8:9 EtOAc:hexanes) to afford aldoxime **18** (32.2 mg, 94% yield) as a white solid.  $R_f = 0.50$  (1:1 EtOAc:hexanes);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.74 (br s, 1H), 7.50 (s, 1H), 7.32 (dd,  $J = 8.2, 7.8$  Hz, 1H), 6.83 (d,  $J = 8.2$  Hz, 1H), 6.82 (d,  $J = 7.8$  Hz, 1H), 5.72 (dd,  $J = 17.4, 10.9$  Hz, 1H), 5.39 (d,  $J = 10.9$  Hz, 1H), 5.15 (d,  $J = 17.4$  Hz, 1H), 4.92 (d,  $J = 7.8$  Hz, 1H), 3.50 (d,  $J = 7.8$  Hz, 1H), 3.20 (s, 3H), 1.60 (s, 3H), 1.44 (s, 3H), 0.85 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  203.6, 202.2, 169.7, 150.4, 144.3, 134.1, 130.8, 130.0, 127.1, 126.6, 119.0, 109.0, 86.1, 78.5, 64.3, 62.8, 60.4, 51.8, 26.7, 25.1, 20.0, 19.2; IR (Neat film, NaCl) 3396, 2928, 1723, 1609, 1585, 1458, 1366, 1143, 1049  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calc'd for  $\text{C}_{22}\text{H}_{22}\text{N}_2\text{O}_5$   $[\text{M}]^+$ : 394.1529, found 394.1536.



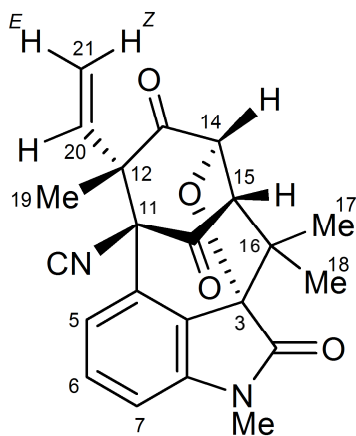
**Isothiocyanate 19.** A 25 mL round-bottomed flask equipped with a magnetic stir bar was charged with oxime **18** (16 mg, 0.0406 mmol, 1.0 equiv) and DMF (0.4 mL). Solid *N*-chlorosuccinimide (6.5 mg, 0.0486 mmol, 1.2 equiv) was added. After 50 min, THF (2 mL) was added and the reaction cooled to 0 °C. After 5 min, solid propylenethiourea **22** (5.7 mg, 0.0486 mmol, 1.2 equiv) was added followed by triethylamine (11  $\mu\text{L}$ , 0.0789 mmol, 1.9 equiv). The reaction was stirred for an additional 10 min at 0 °C, at which point it was quenched by the addition of water and was extracted with 1:1 EtOAc:hexanes (3 x 10 mL). Combined organic layers were washed with water (2 x 10 mL). The crude residue was purified via preparative thin-layer chromatography (6 cm x 10 cm, 1:1 EtOAc:hexanes) to afford isothiocyanate **19** (10.8 mg, 65% yield) as a white solid.  $R_f = 0.65$  (1:1 EtOAc:hexanes);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.40 (app t,  $J = 8.0$  Hz, 1H), 7.25 (dd,  $J = 8.0, 0.7$  Hz, 1H), 6.87 (dd,  $J = 8.0, 0.7$  Hz, 1H), 5.51 (dd,  $J = 17.2, 10.7$  Hz, 1H), 5.39 (d,  $J = 10.7$  Hz, 1H), 5.30 (d,  $J = 17.2$  Hz, 1H), 4.96 (d,  $J = 7.5$  Hz, 1H), 3.57 (d,  $J = 7.5$  Hz, 1H), 3.22 (s, 3H), 1.60 (s, 3H), 1.37 (s, 3H), 0.83 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  201.5, 195.4, 169.8, 143.8, 142.1, 133.5, 130.8, 129.1, 125.1, 124.1, 119.9, 109.7, 86.3, 82.3, 79.4, 62.6, 61.7, 53.3, 26.9, 25.0, 19.8, 19.8; IR (Neat film, NaCl) 2978, 2930, 2040, 1730, 1608, 1590, 1462, 1365, 1344, 1045  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calc'd for  $\text{C}_{22}\text{H}_{20}\text{N}_2\text{O}_4\text{S}$  [ $\text{M}^+$ ] $^+$ : 408.1144, found 408.1147.



**Welwitindolinone D isonitrile (5).** Preparation of oxazaphospholidine **23**: A two-necked 50 mL flask equipped with a magnetic stir bar and a reflux condenser (air-cooled) was charged with *N*-

methylaminoethanol (0.4 mL, 5 mmol) and triethyl amine (1.4 mL, 10 mmol). The flask was immersed in a water bath. A solution of dichlorophenylphosphine (0.68 mL, 5 mmol) in 5 mL toluene was added dropwise over 5 min (slow addition is recommended to avoid vigorous reaction). After 5 min of stirring, the thick white reaction mixture was placed in a preheated 100 °C oil-bath. After 1 h the above mixture was removed from the oil-bath and cooled to ambient temperature and diluted with 5 mL of toluene. The white suspension was shaken until homogeneous and used without further purification.

A 1 mL V-vial with an attached condenser was charged with isothiocyanate **19** (1.0 mg, 0.0024 mmol, 1.0 equiv) and toluene (0.1 mL). Freshly prepared solution of oxazaphospholidine **23** (0.2 mL) was added and the reaction was heated to 110 °C in an oil bath. After 1 h, the reaction was cooled to ambient temperature, diluted with EtOAc and filtered over a 4 cm Celite plug and which was then washed with EtOAc. The crude reaction mixture was concentrated and purified by preparative thin layer chromatography (4 cm x 10 cm) with 2:3 EtOAc:hexanes as the solvent system. *N*-methylwelwitindolinone D isonitrile (**5**) was isolated (0.5 mg, 54%) as a white solid.  $R_f = 0.62$  (1:1 EtOAc:hexanes);  $^1\text{H NMR}$  (500 MHz,  $\text{CD}_2\text{Cl}_2$ , referenced at 5.32 ppm)  $\delta$  7.45 (app t,  $J = 8.3$  Hz, 1H), 7.29 (dd,  $J = 8.3, 0.8$  Hz, 1H), 6.93 (dd,  $J = 7.9, 0.8$  Hz, 1H), 5.48 (dd,  $J = 16.3, 10.6$  Hz, 1H), 5.43 (dd,  $J = 10.6, 1.7$  Hz, 1H), 5.36 (dd,  $J = 16.3, 1.7$  Hz, 1H), 4.92 (d,  $J = 7.5$  Hz, 1H), 3.57 (d,  $J = 7.5$  Hz, 1H), 3.19 (s, 3H), 1.55 (s, 3H), 1.39 (s, 3H), 0.80 (s, 3H);  $^{13}\text{C NMR}$  (125 MHz,  $\text{CD}_2\text{Cl}_2$ , referenced at 53.8 ppm)  $\delta$  201.2, 192.8, 169.8, 165.5, 144.4, 133, 131.3, 126.8, 126.7, 123.9, 120.6, 110.5, 79.6, 62, 61.6, 27.1, 25, 20.1, 19.7 (resonances for C3 and C11 were below the threshold of detection; C16 overlaps with the  $\text{CD}_2\text{Cl}_2$  resonance); IR (Neat flm, NaCl) 2927, 2138, 1731, 1609, 1590, 1463, 1366, 1344 1193, 1141, 1016, 955  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calc'd for  $\text{C}_{22}\text{H}_{20}\text{N}_2\text{O}_4$  [ $\text{M}^+$ ]: 376.1423, found 376.1430.

**Table S1.**  $^1\text{H}$  NMR of **5**, 500 MHz,  $\text{CD}_2\text{Cl}_2$ *N*-Methylwelwitindolinone D  
Isonitrile (**5**)

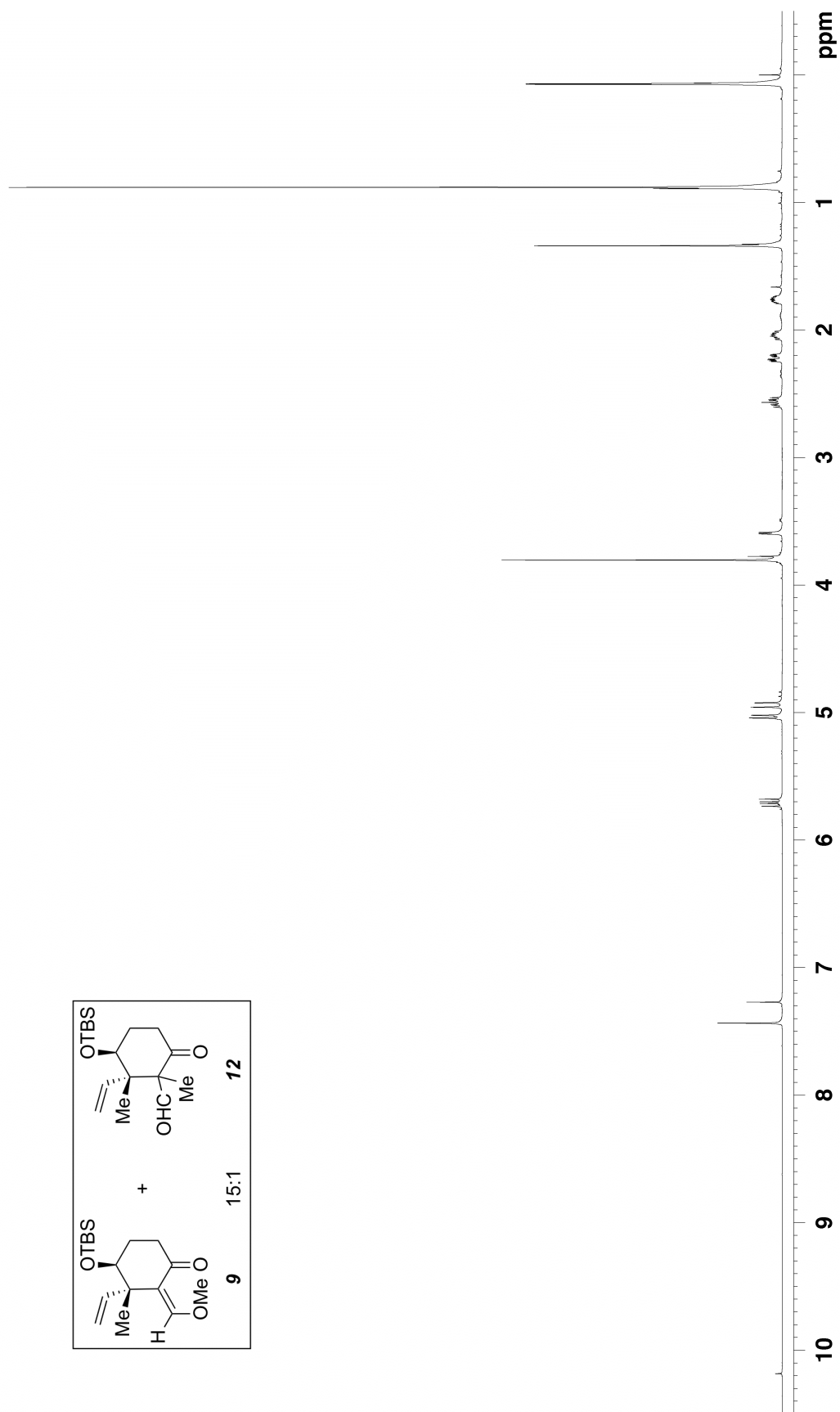
Position	Synthetic	Reported <sup>6</sup>
NMe	3.19, s, 3H	3.19, s, 3H
5	7.29, dd, 8.3/0.8, 1H	7.29, dd, 8.3/0.7, 1H
6	7.45, app t, 8.1, 1H	7.45, dd, 8.3/7.8, 1H
7	6.93, dd, 7.8/0.8, 1H	6.93, dd, 7.8/0.7, 1H
14	4.92, d, 7.5, 1H	4.92, d, 7.5, 1H
15	3.57, d, 7.5, 1H	3.57, d, 7.5, 1H
17	1.55, s, 3H	1.55, s, 3H
18	0.80, s, 3H	0.80, s, 3H
19	1.39, s, 3H	1.39, s, 3H
20	5.48, dd, 16.3/10.6, 1H	5.47, dd, 16/11, 1H
21 <sup>E</sup>	5.43, dd, 10.6/1.7, 1H	5.36, <sup>7</sup> dd, 11/1.6, 1H
21 <sup>Z</sup>	5.36, dd, 16.3/1.7, 1H	5.43, <sup>7</sup> dd, 16/1.6, 1H

<sup>6</sup> Spectral information is provided only in tabular form. Jimenez, J. I.; Huber, U.; Moore, R. E.; Patterson, G. M. L. *J. Nat. Prod.* **1999**, *62*, 569–572.

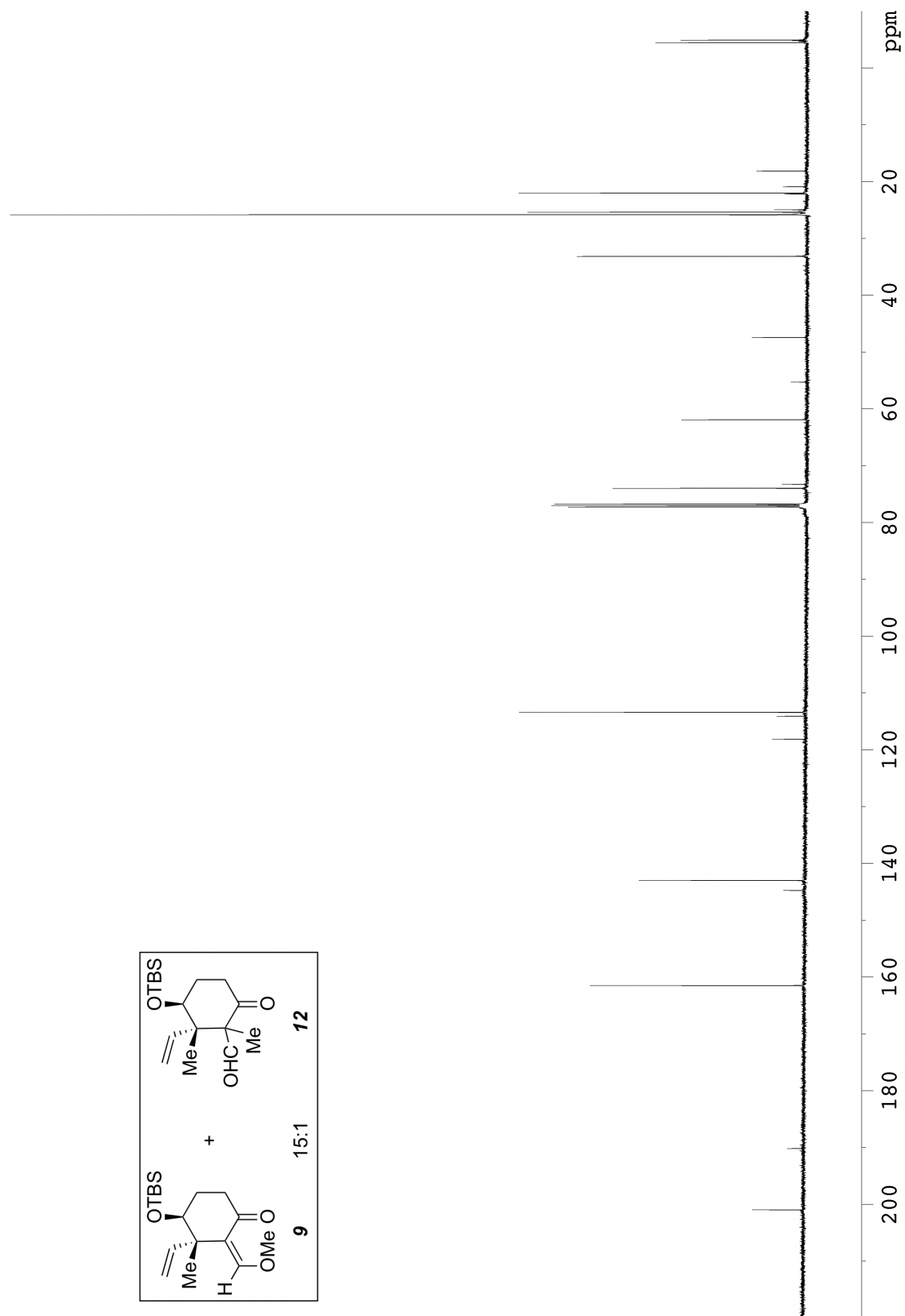
<sup>7</sup> Presumably, this discrepancy is due to a typographical error in the isolation report.

**Reference 5s from the manuscript:**

Freeman, D. B.; Holubec, A. A.; Weiss, W. M.; Dixon, J. A.; Kakefuda, A.; Ohtsuka, M.; Inoue, M.; Vaswani, R. G.; Ohki, H.; Doan, B. D.; Reisman, S. E.; Stoltz, B. M.; Day, J. J.; Tao, R. N.; Dieterich, N. A.; Wood, J. L. *Tetrahedron* **2010**, *66*, 6647–6655.

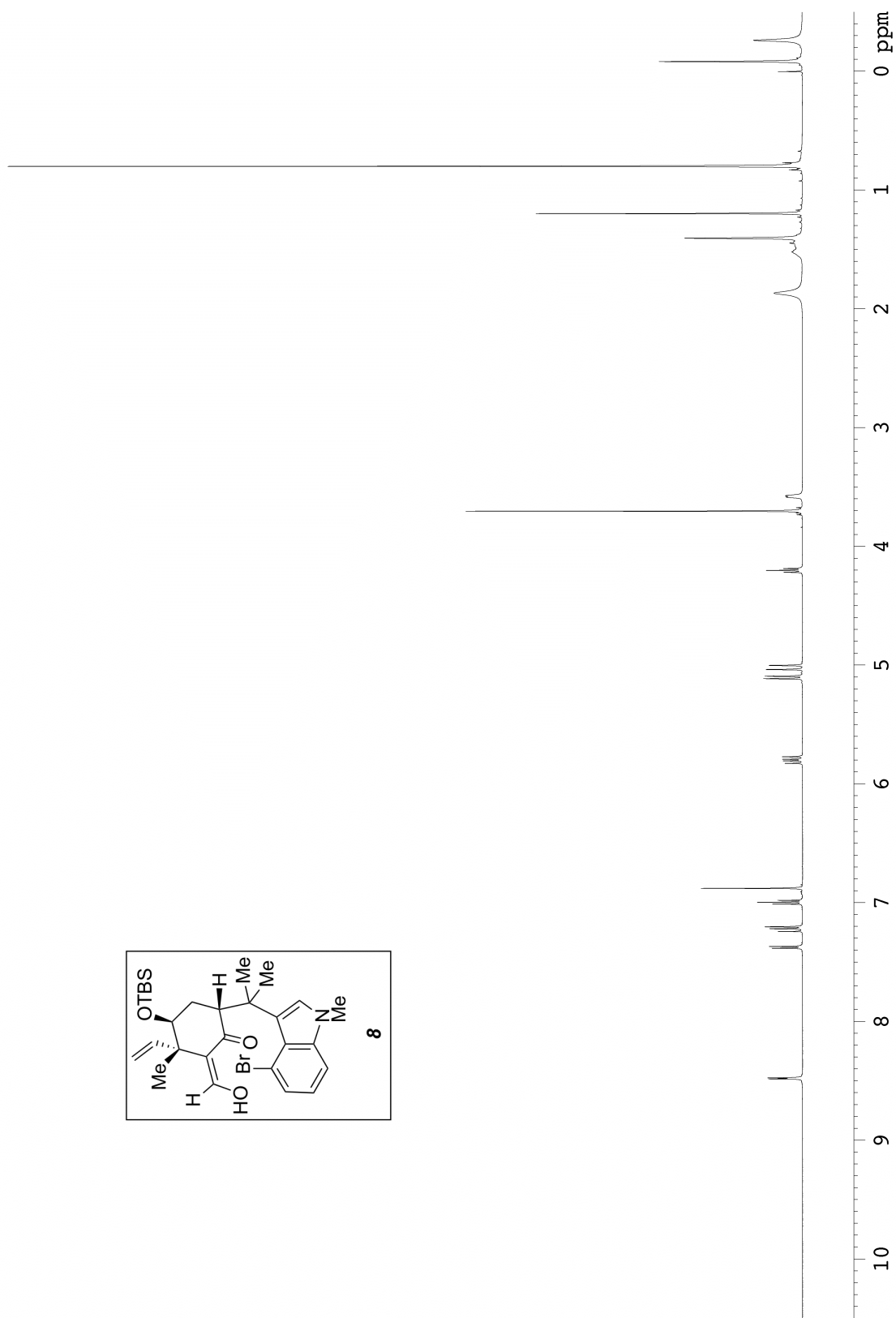


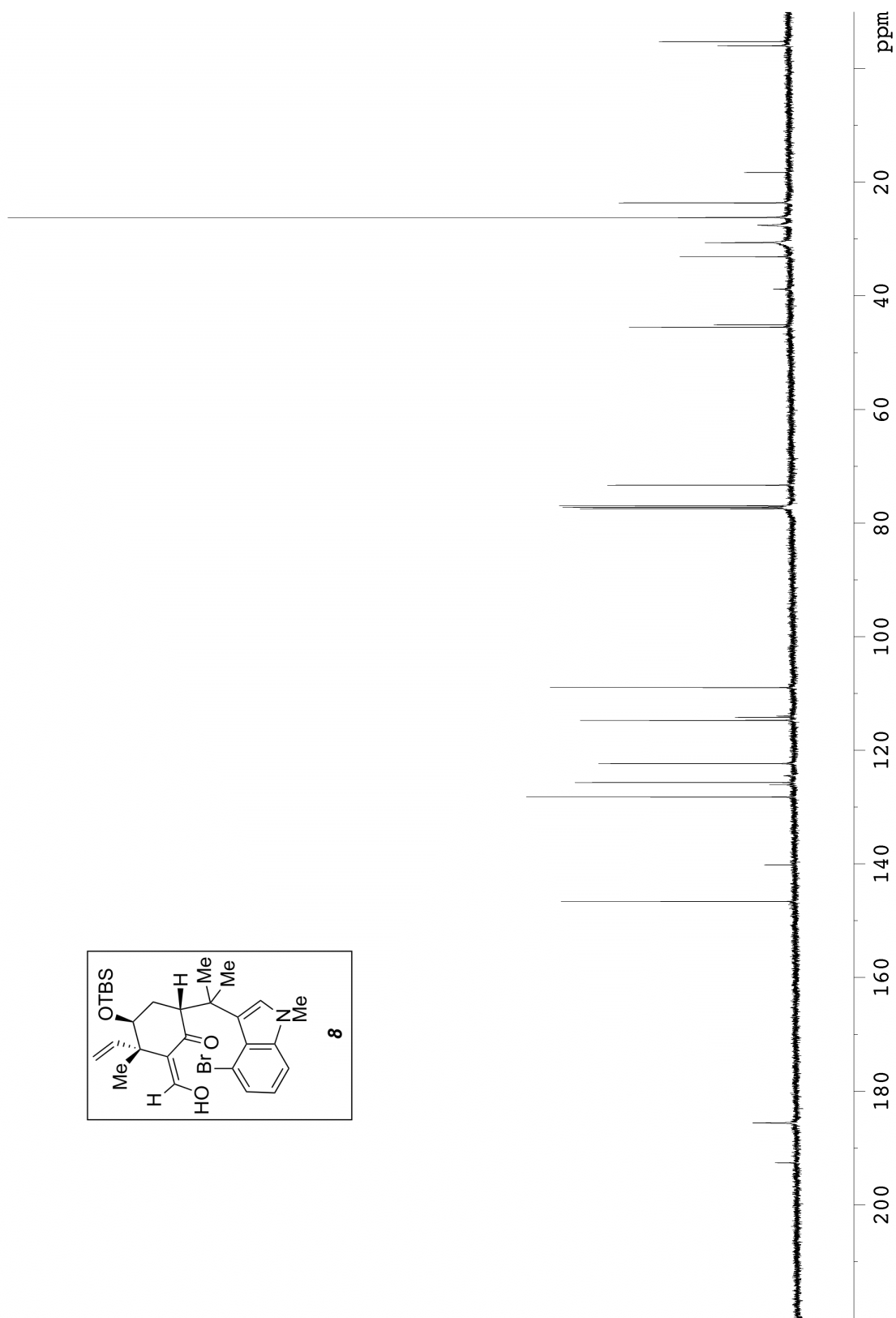
**Figure S1.1.** <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) of vinyllogous ester **9** and β-ketoaldehyde **12**.



**Figure S1.2.**  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ) of vinyllogous ester **9** and  $\beta$ -ketoaldehyde **12**.







**Figure S2.2.**  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ) of vinyllogous acid **8**.

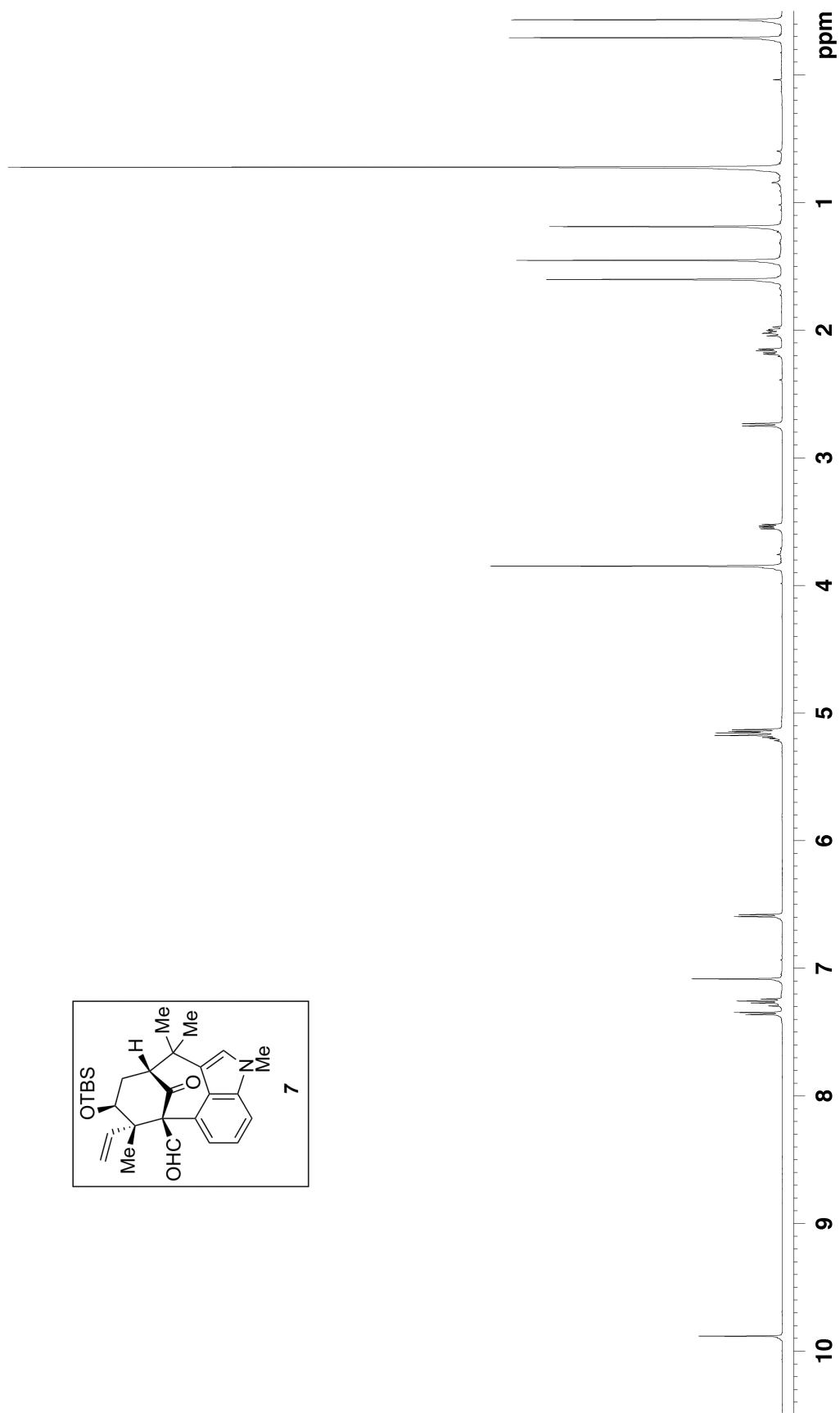
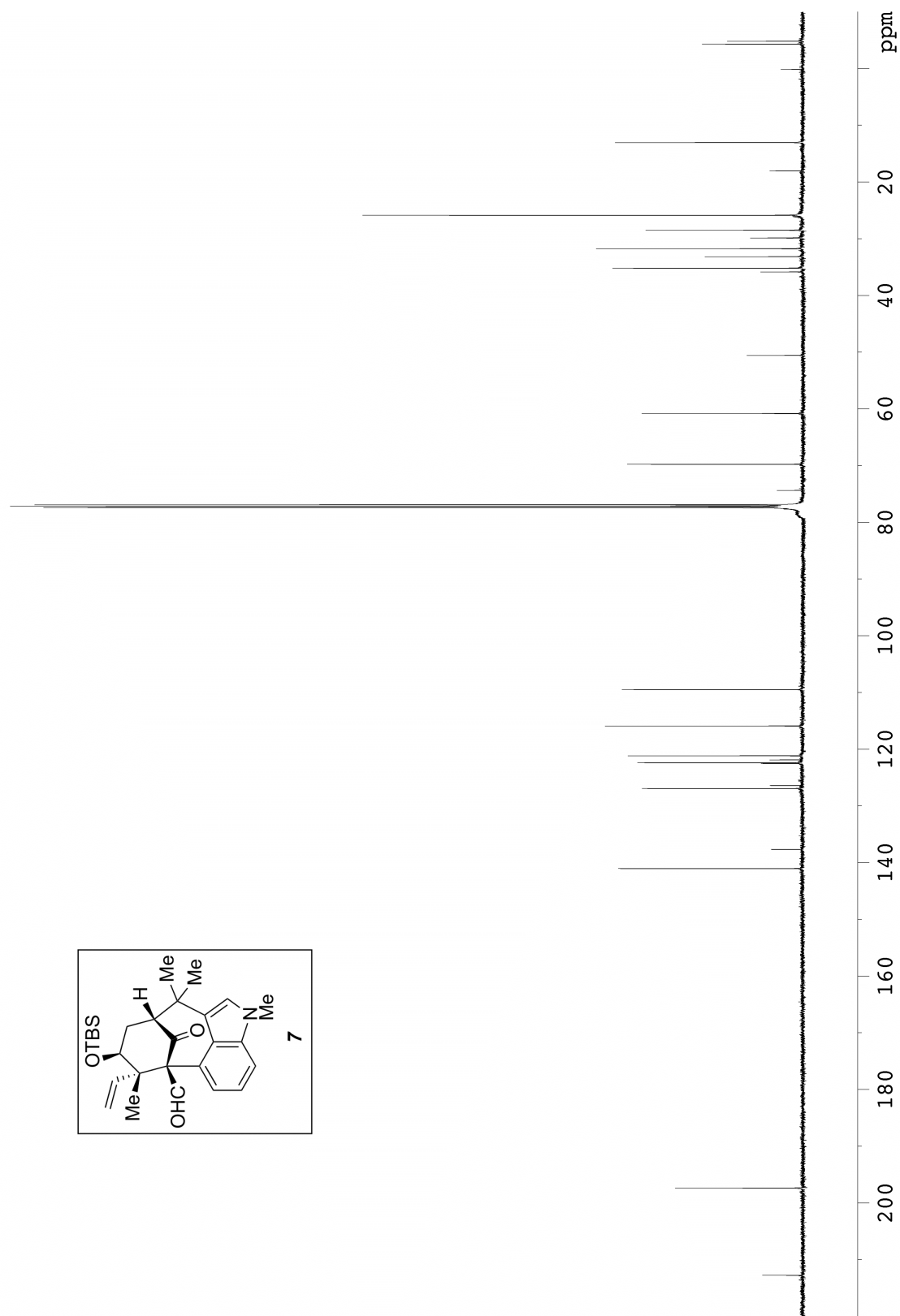
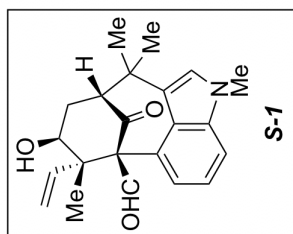
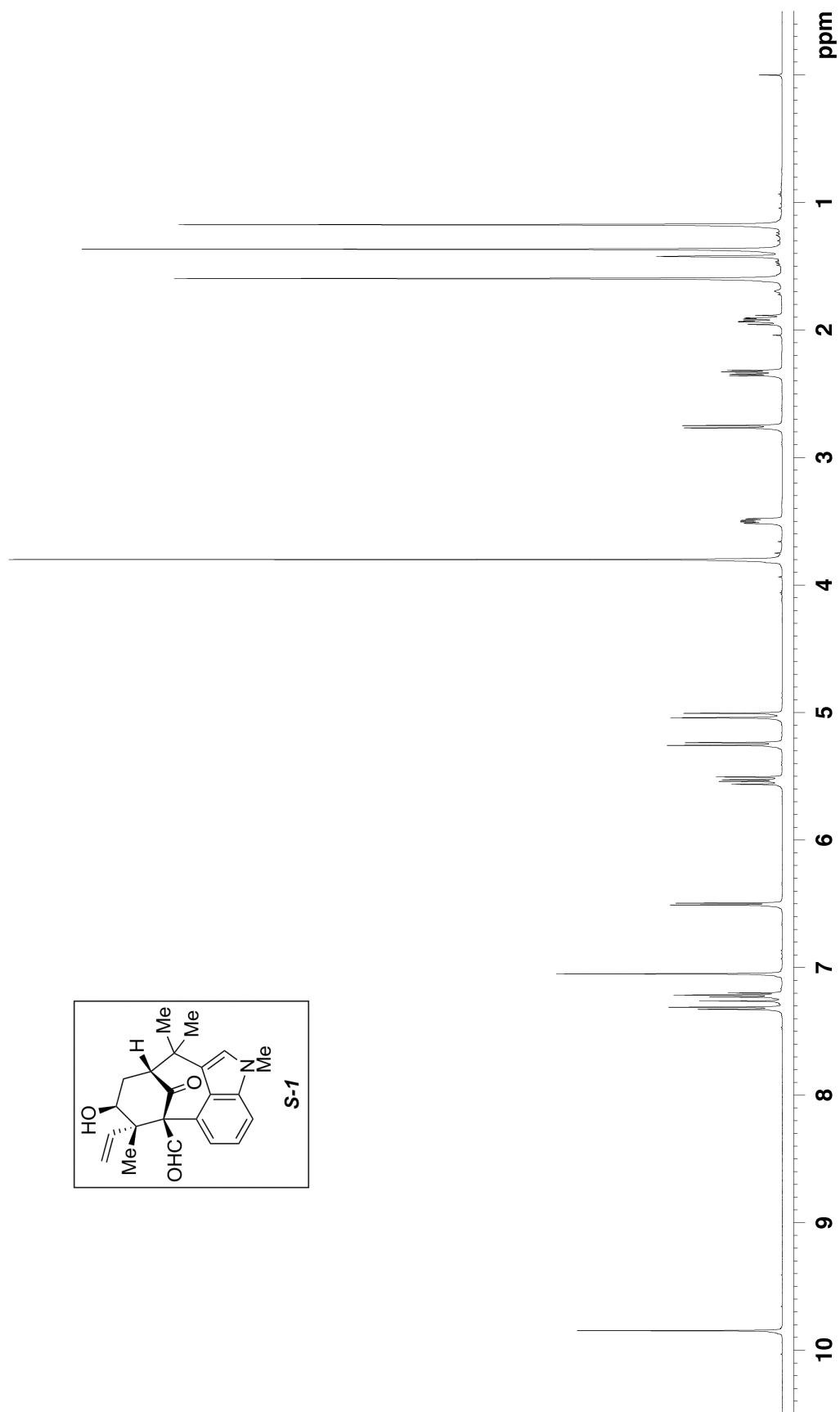


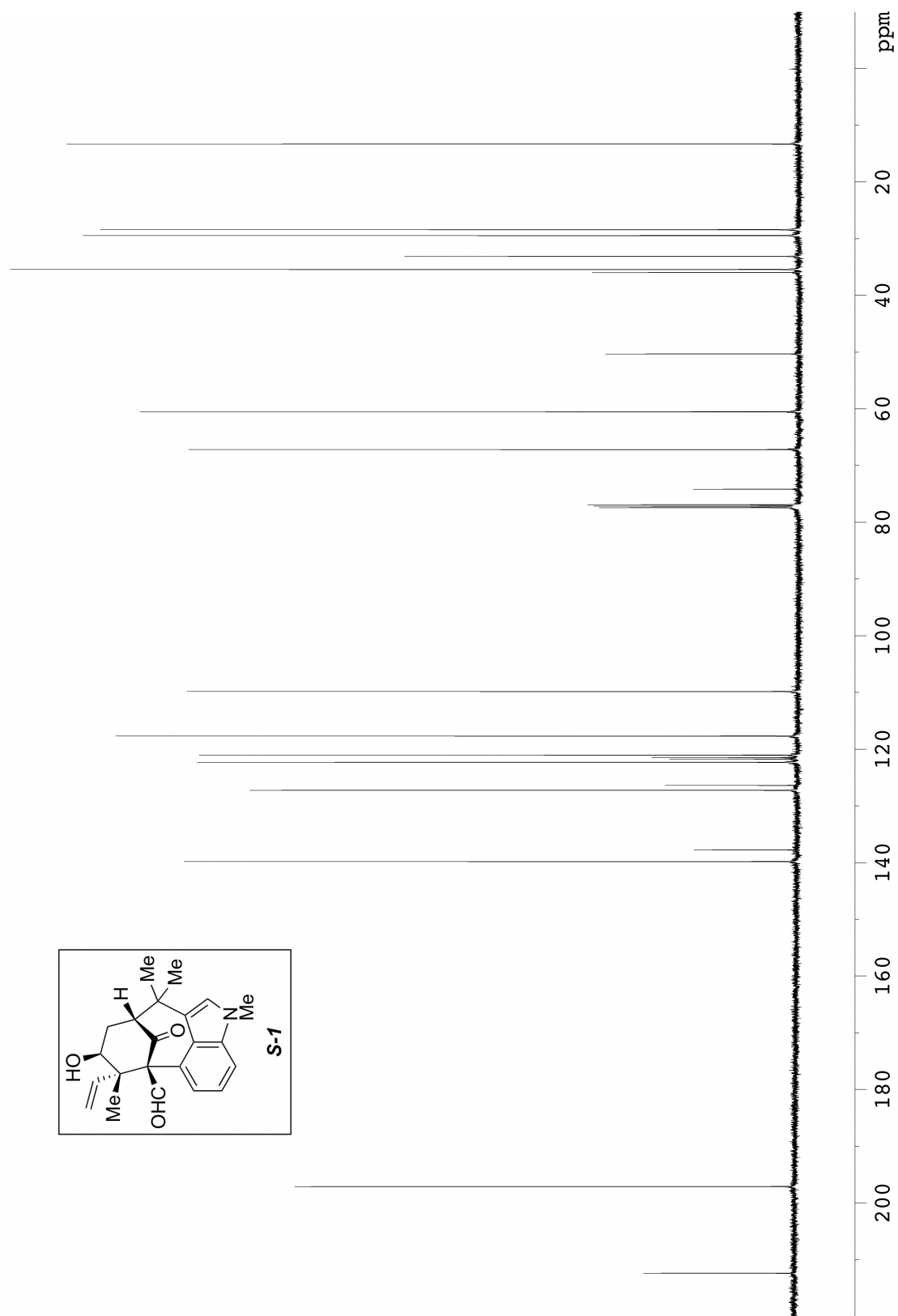
Figure S3.1. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) of tetracycle 7.

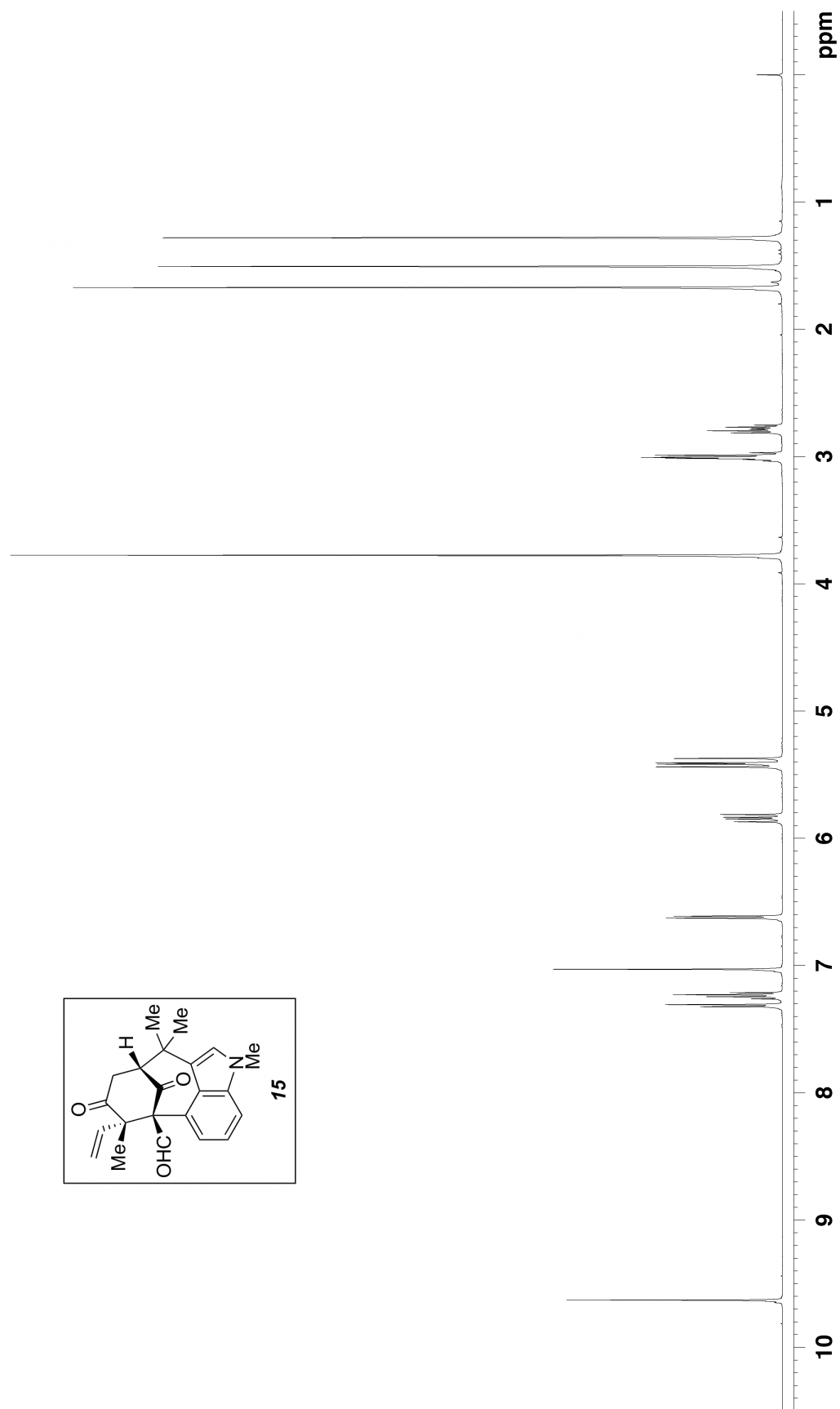


**Figure S3.2.**  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ) of tetracycle 7.

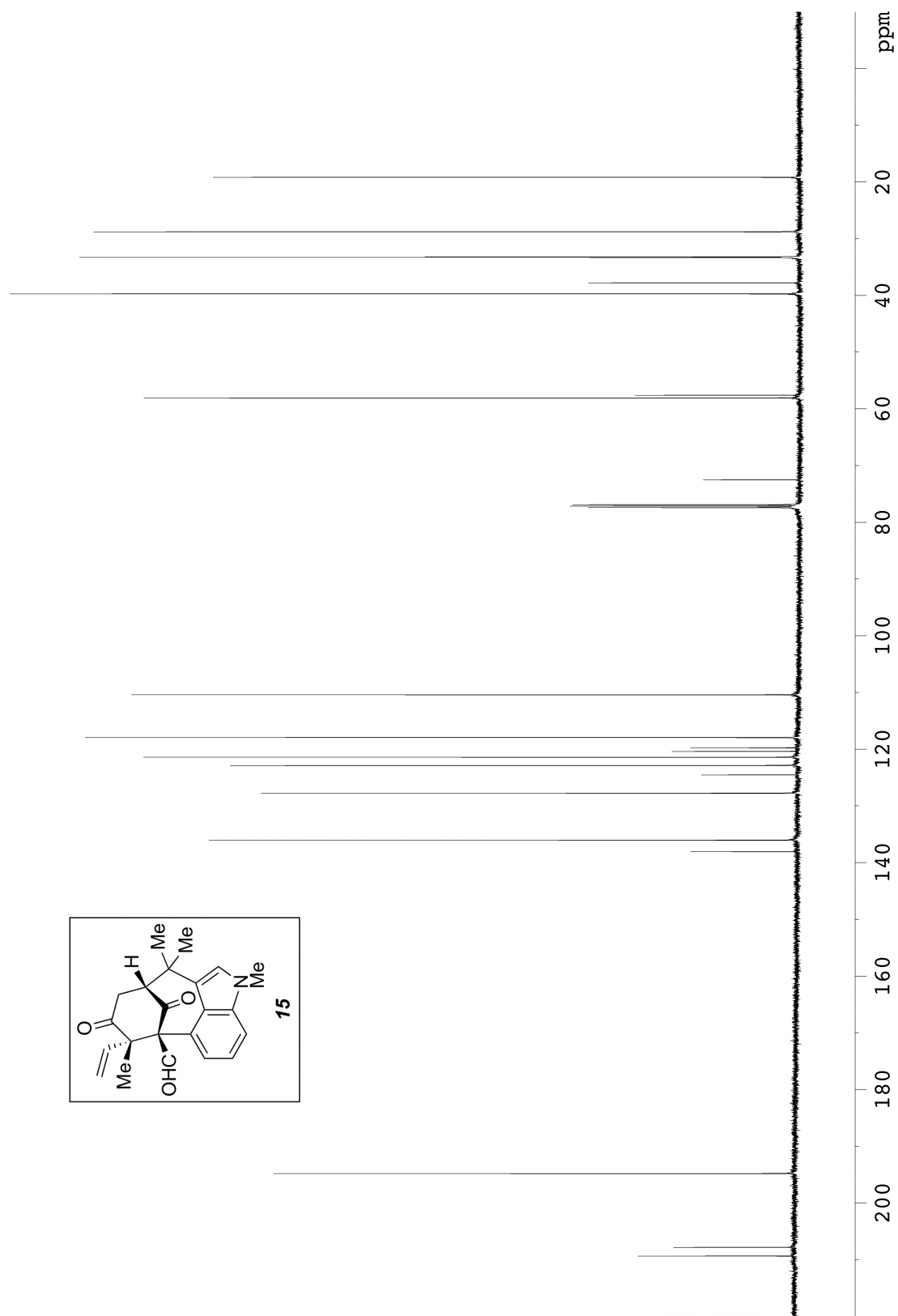


**Figure S4.1.** <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) of alcohol **S-1**.

**Figure S4.2.** <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) of alcohol **S-1**.

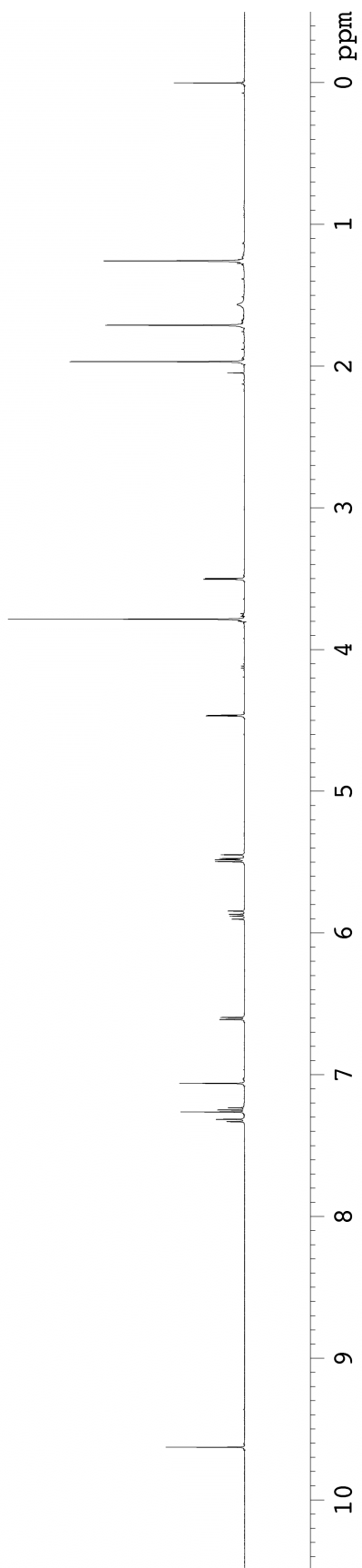
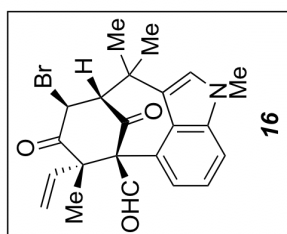


**Figure S5.1.**  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) of dione **15**.

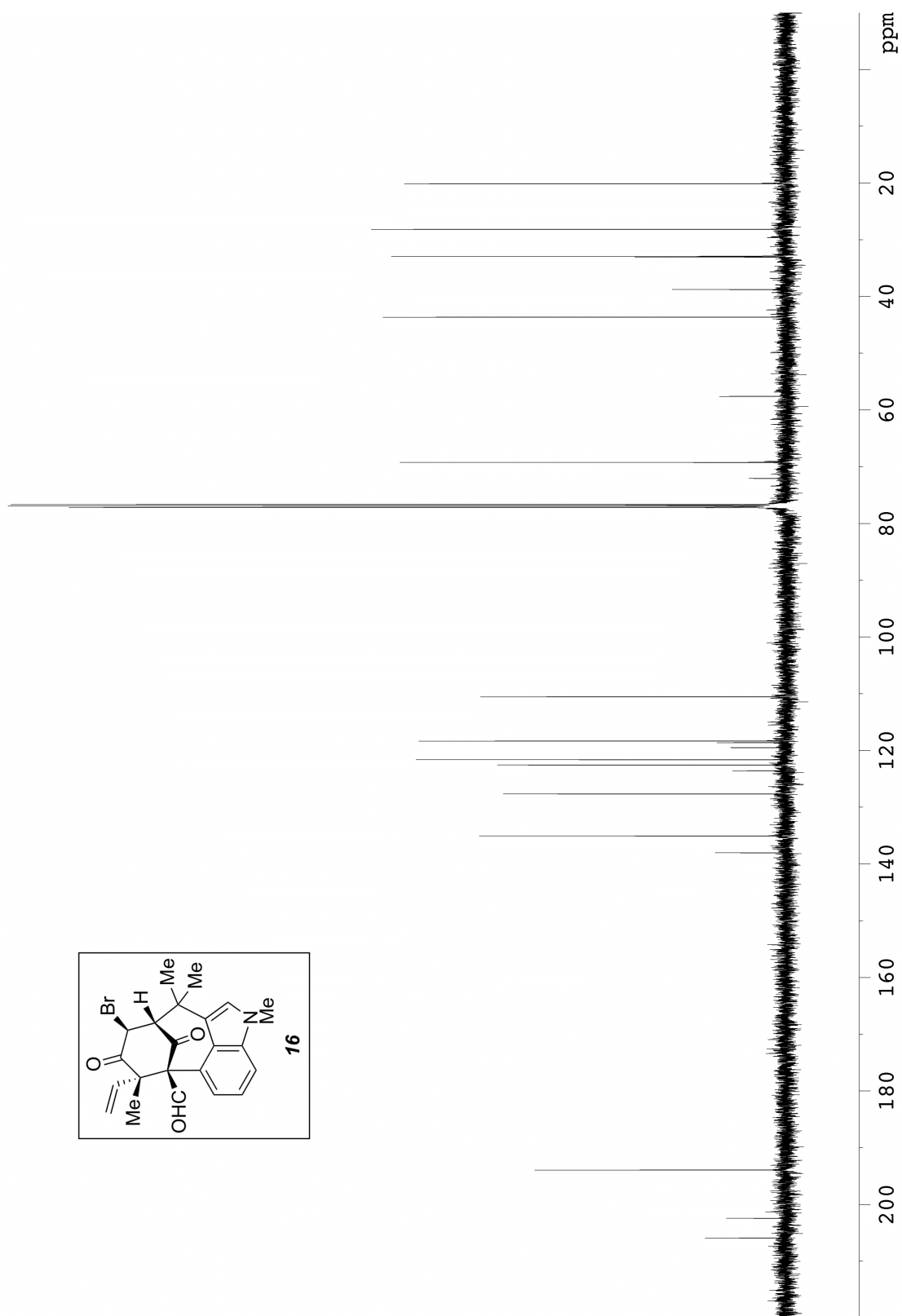


**Figure S5.2.**  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ) of dione **15**.

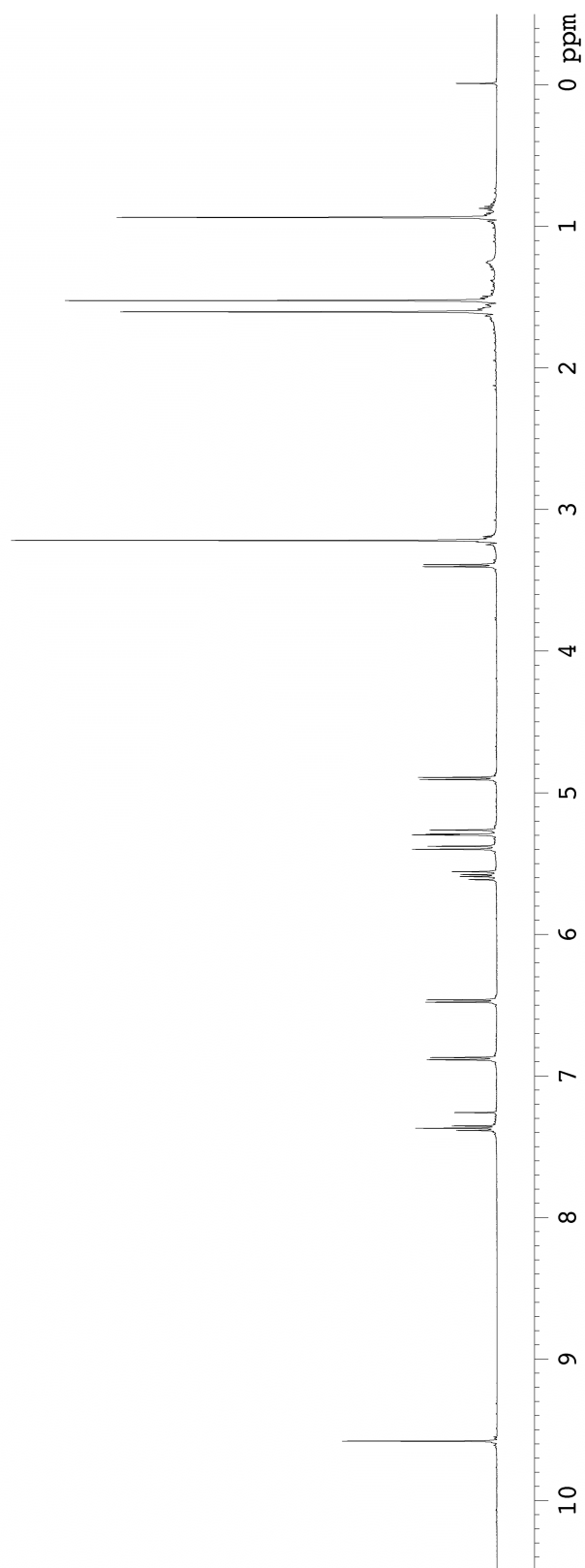
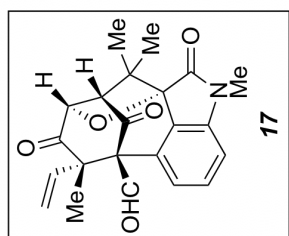




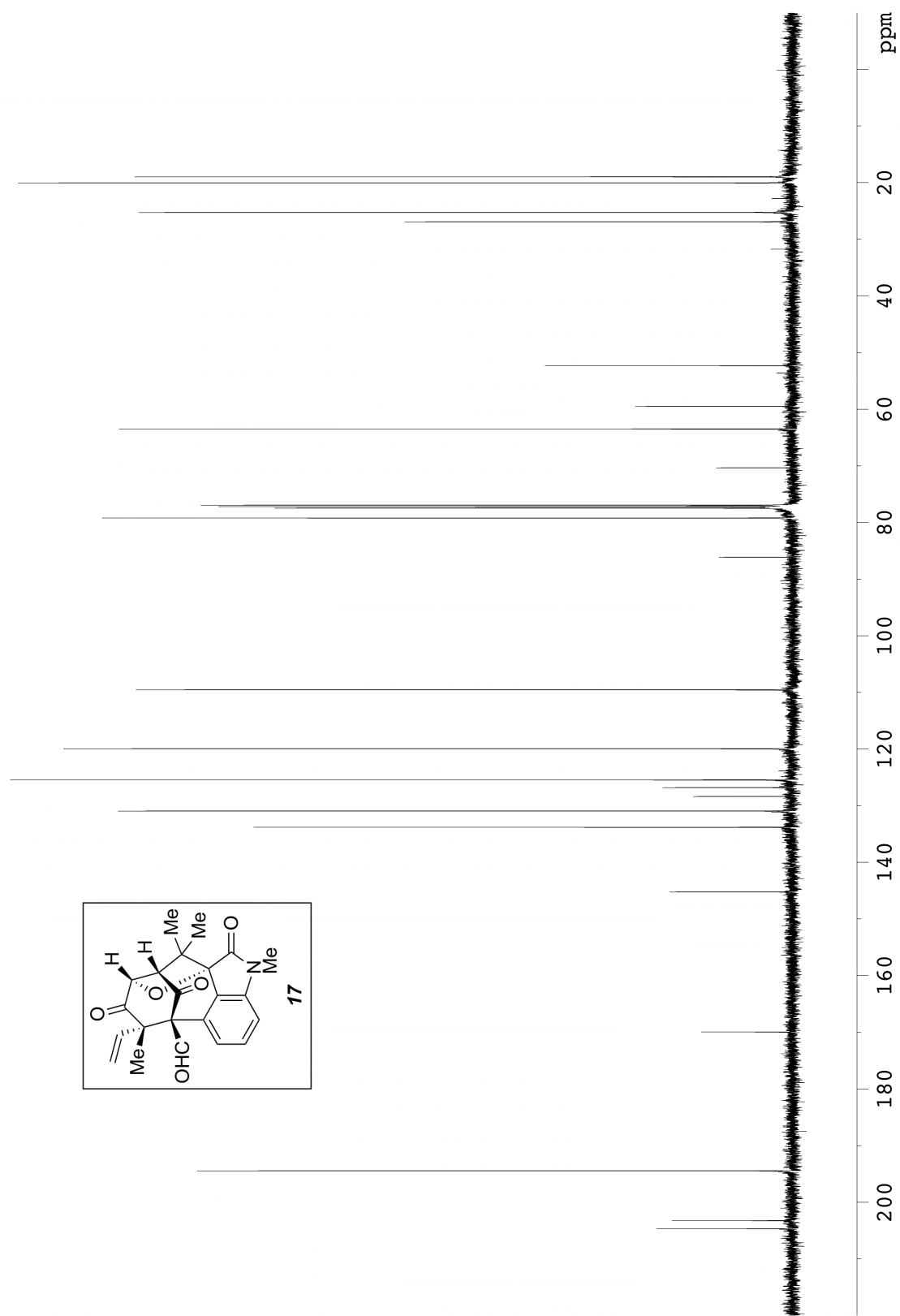
**Figure S6.1.** <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) of bromodione **16**.



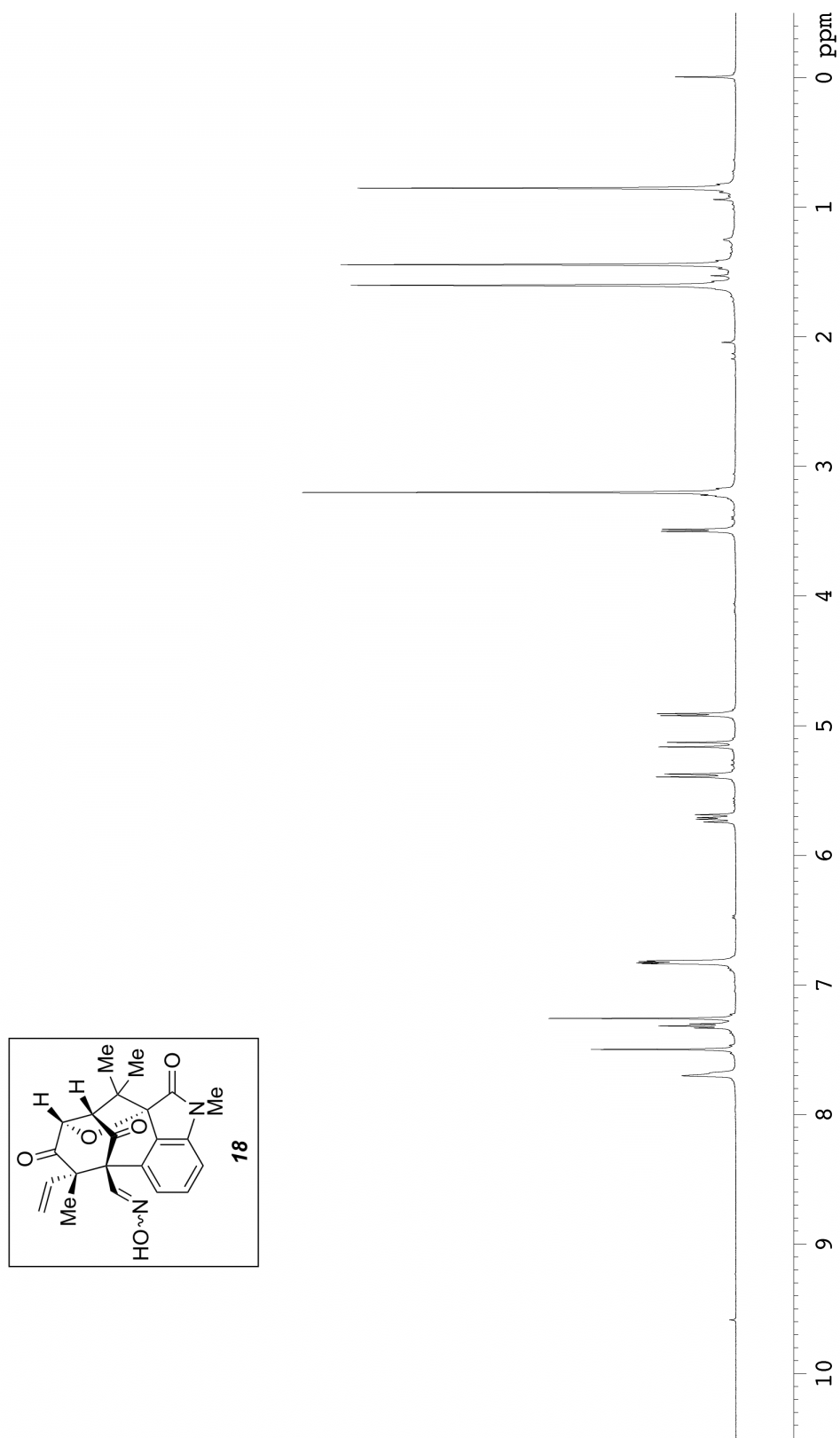
**Figure S6.2.**  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ) of bromodione **16**.



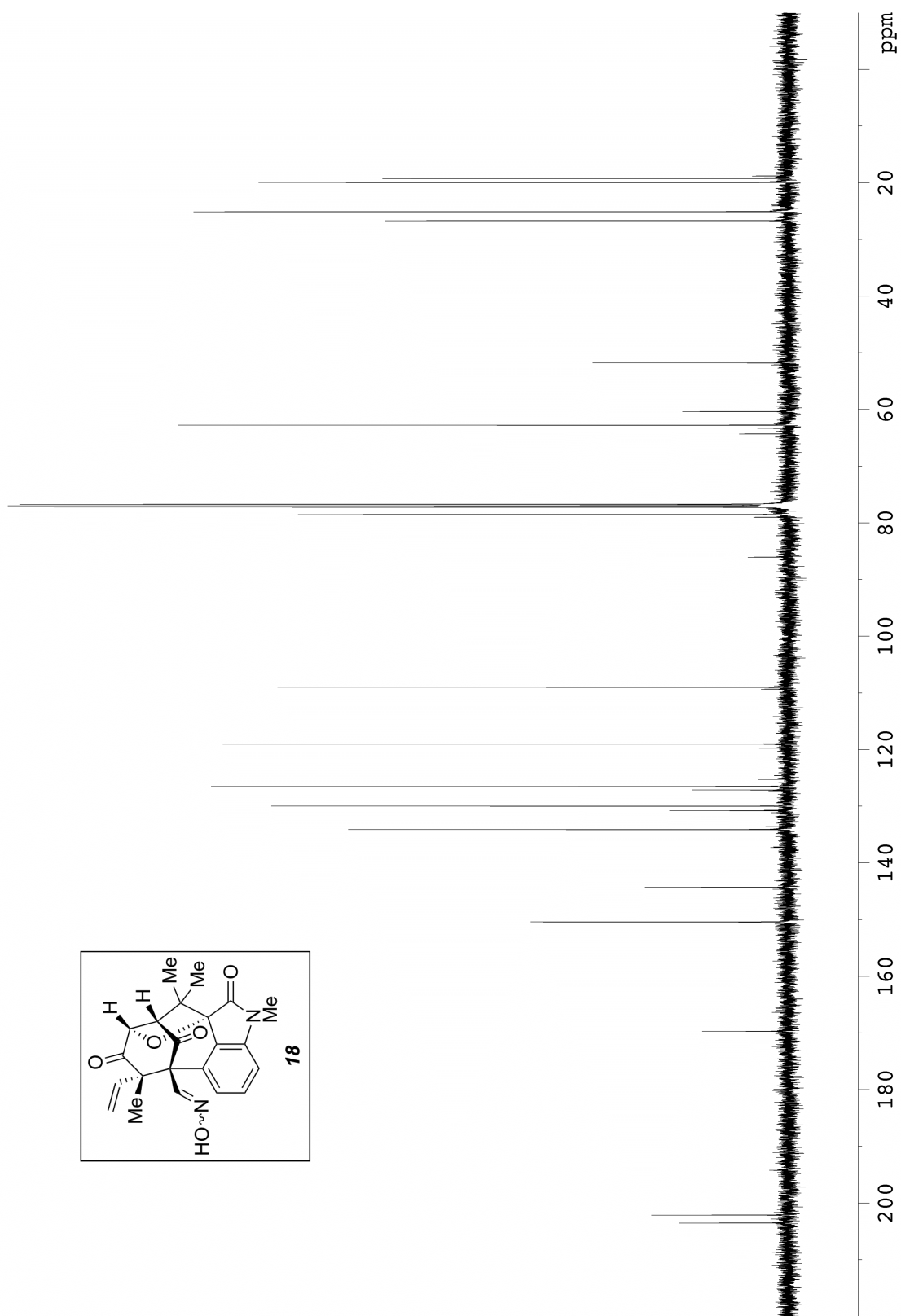
**Figure S7.1.** <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) of cyclic ether **17**.



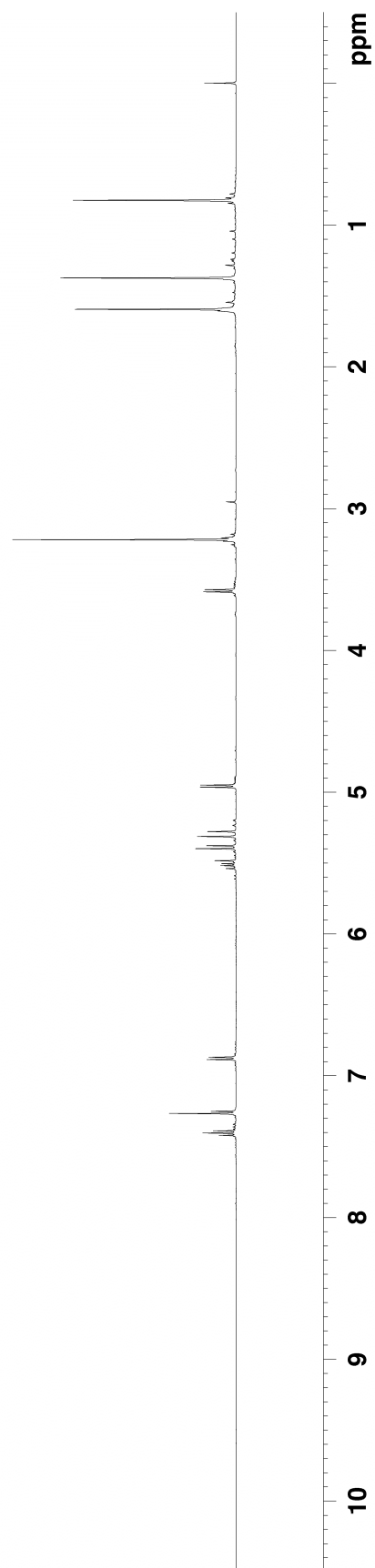
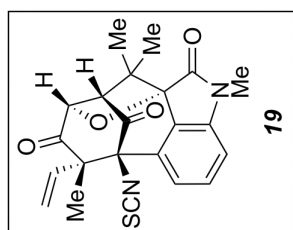
**Figure S7.2.**  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ) of cyclic ether **17**.



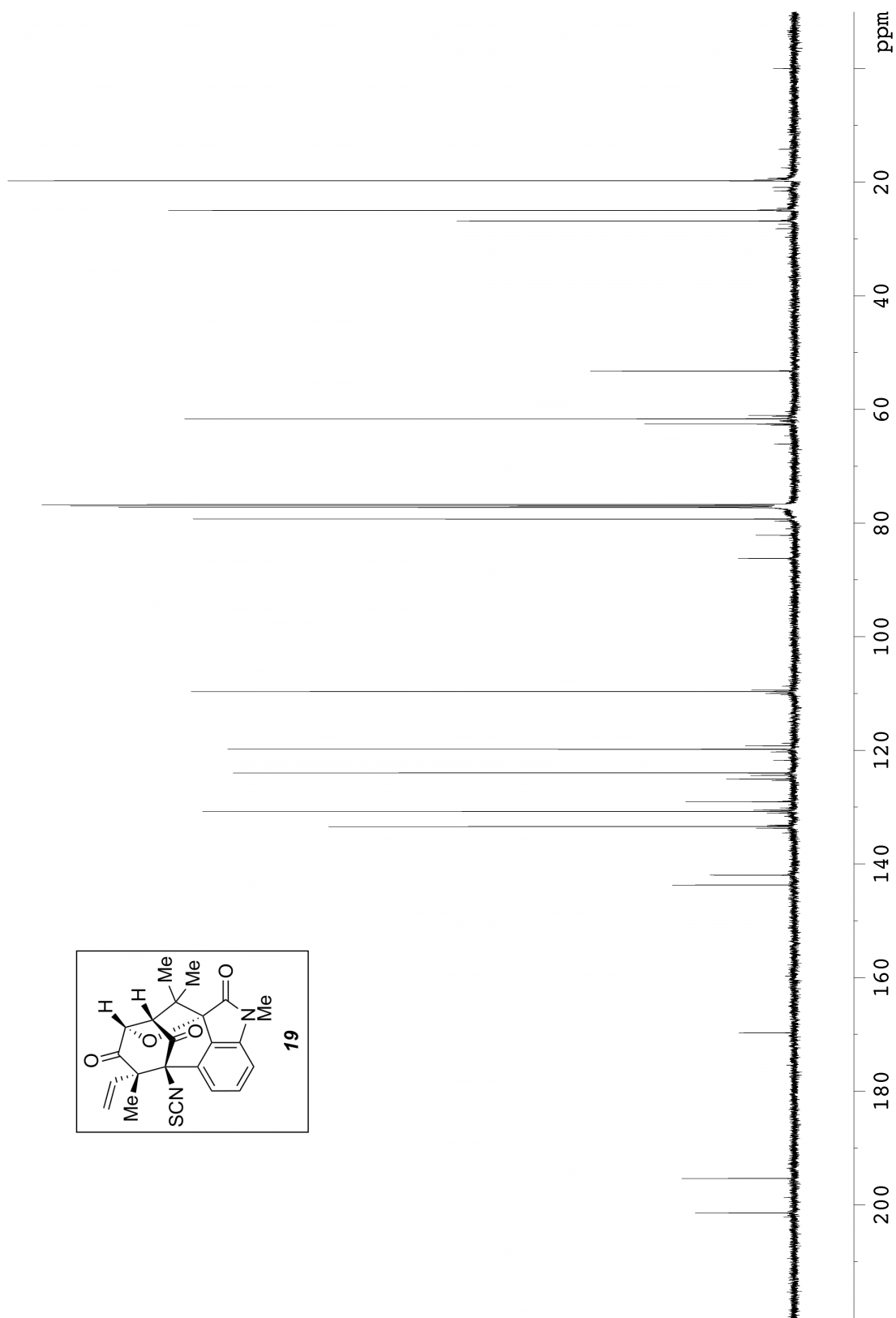
**Figure S8.1.** <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) of aldoxime **18**.



**Figure S8.2.**  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ) of aldoxime **18**.

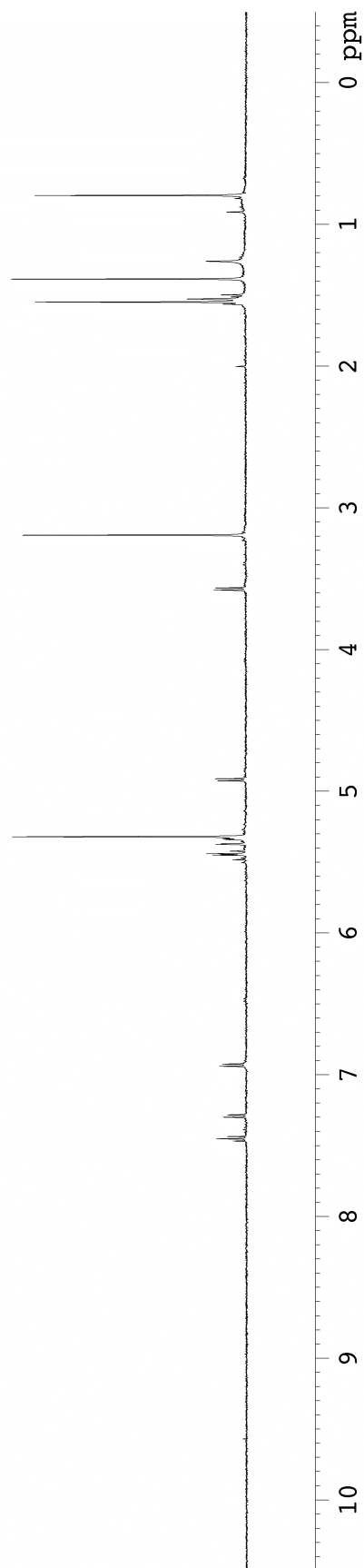
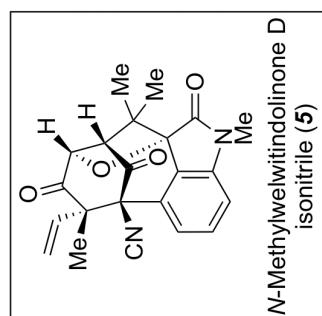


**Figure S9.1.** <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) of isothiocyanate **19**.

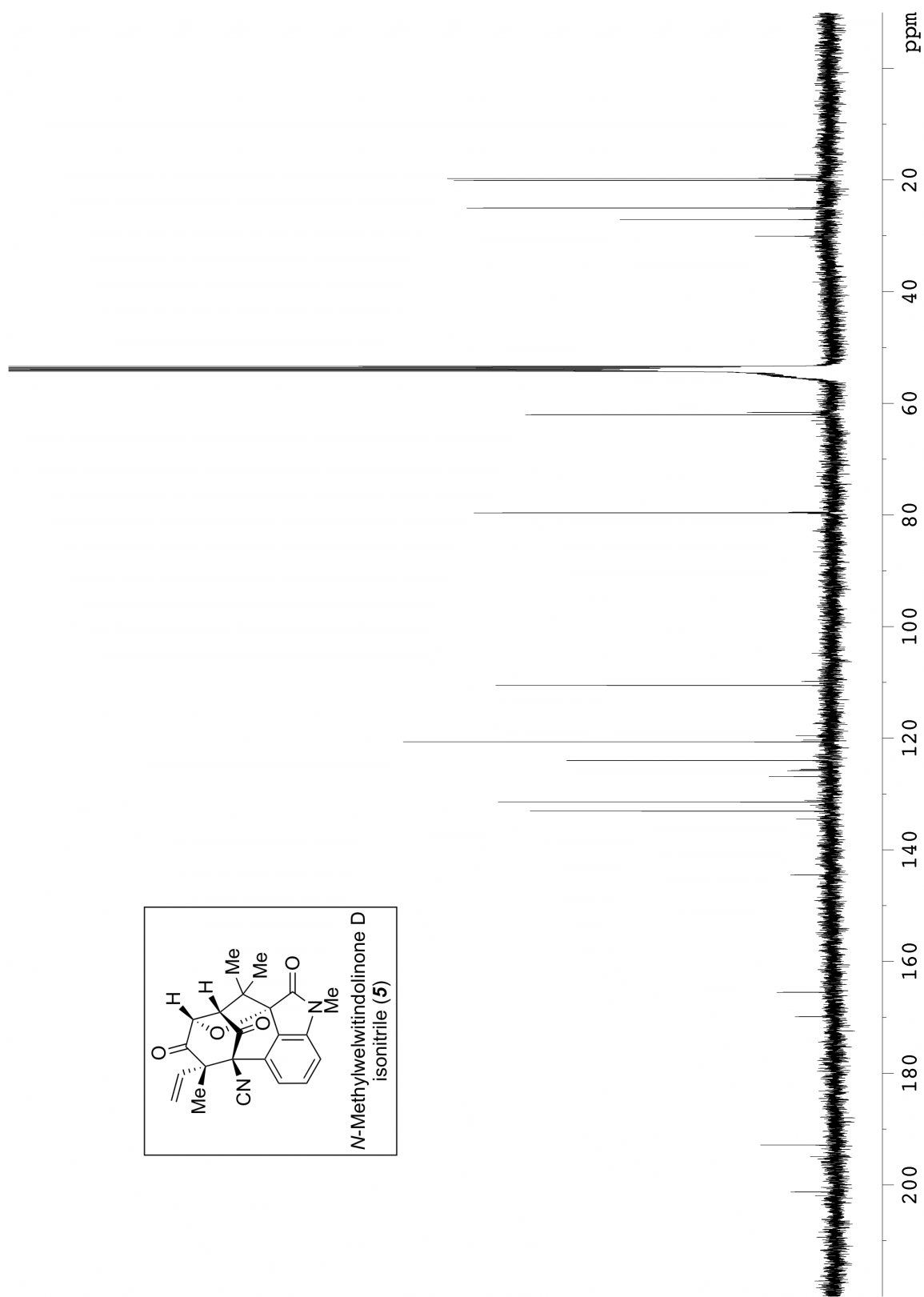


**Figure S9.2.**  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ) of isothiocyanate **19**.

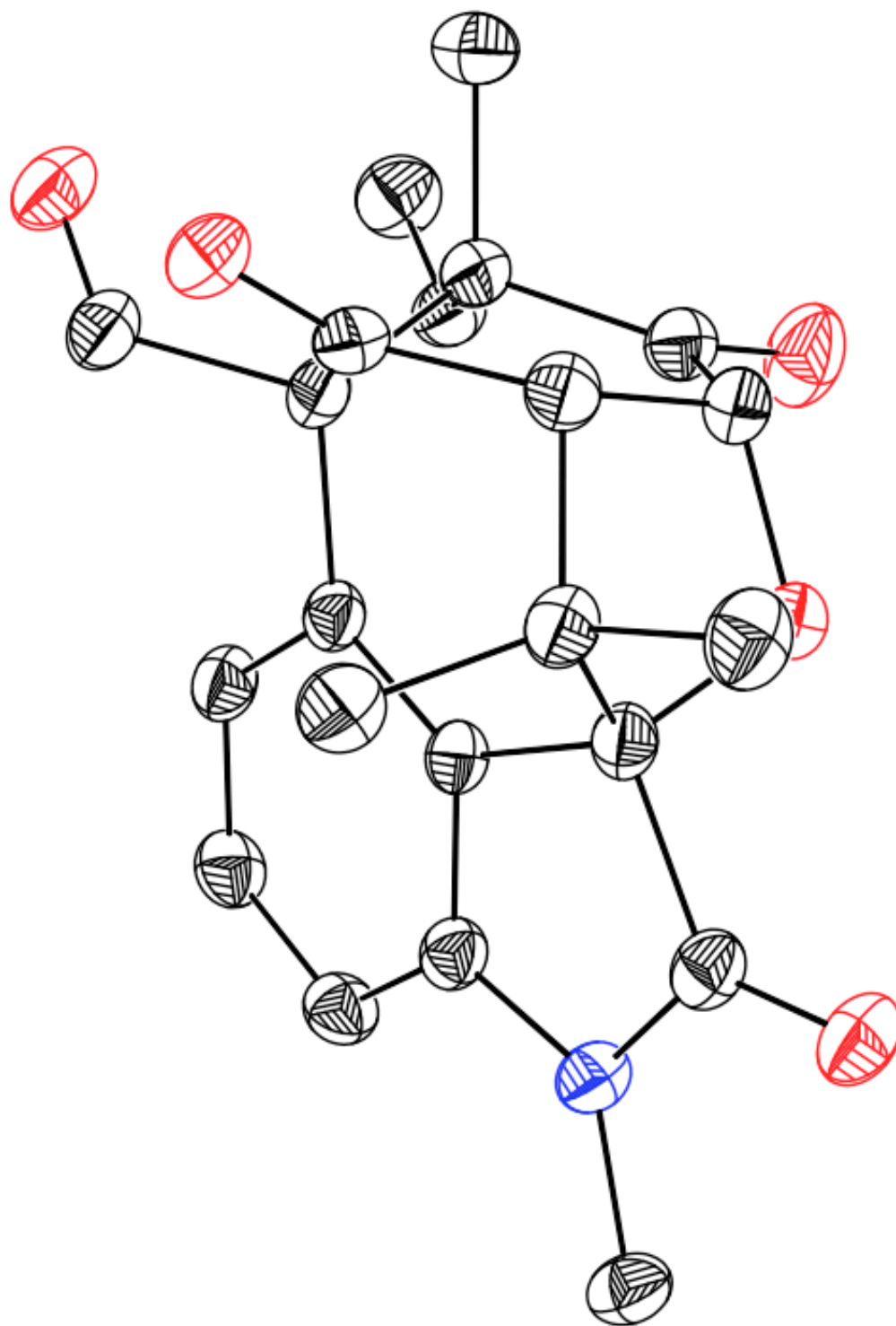




**Figure S10.1.**  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_2\text{Cl}_2$ ) of *N*-methylwelwitindolinone D isonitrile (**5**).



**Figure S10.2.**  $^{13}\text{C}$  NMR (125 MHz,  $\text{CD}_2\text{Cl}_2$ ) of *N*-methylwelwitindolinone D isonitrile (**5**).

**Figure S11.** ORTEP drawing of cyclic ether **17** (shown with 50% probability ellipsoids).

## Crystallographic Experimental Section

### Data Collection

An irregular broken fragment (0.24 x 0.24 x 0.20 mm) was selected under a stereo-microscope while immersed in Fluorolube oil to avoid possible reaction with air. The crystal was removed from the oil using a tapered glass fiber that also served to hold the crystal for data collection. The crystal was mounted and centered on a Bruker SMART APEX system at 100 K. Rotation and still images showed the diffractions to be sharp. Frames separated in reciprocal space were obtained and provided an orientation matrix and initial cell parameters. Final cell parameters were obtained from the full data set.

A “full sphere” data set was obtained which samples approximately all of reciprocal space to a resolution of 0.75 Å using 0.3° steps in  $\omega$  using 10 second integration times for each frame. Data collection was made at 100 K. Integration of intensities and refinement of cell parameters were done using SAINT [1]. Absorption corrections were applied using SADABS [1] based on redundant diffractions.

### Structure solution and refinement

The space group was determined as  $P2_1/c$  based on systematic absences and intensity statistics. Direct methods were used to locate most C atoms from the E-map. Repeated difference Fourier maps allowed recognition of all expected C, N and O atoms. Following anisotropic refinement of all non-H atoms, ideal H-atom positions were calculated. Final refinement was anisotropic for all non-H atoms, and isotropic-riding for H atoms. No anomalous bond lengths or thermal parameters were noted. All ORTEP diagrams have been drawn with 50% probability ellipsoids.

### Equations of interest:

$$R_{\text{int}} = \frac{\sum |F_o^2 - \langle F_o^2 \rangle|}{\sum |F_o^2|}$$

$$R1 = \frac{\sum ||F_o| - |F_c||}{\sum |F_o|}$$

$$wR2 = \left[ \frac{\sum [w (F_o^2 - F_c^2)^2]}{\sum [w (F_o^2)^2]} \right]^{1/2}$$

$$\text{Goof} = S = \left[ \frac{\sum [w (F_o^2 - F_c^2)^2]}{(n-p)} \right]^{1/2}$$

$$\text{where: } w = \frac{q}{\sigma^2 (F_o^2) + (aP)^2 + bP};$$

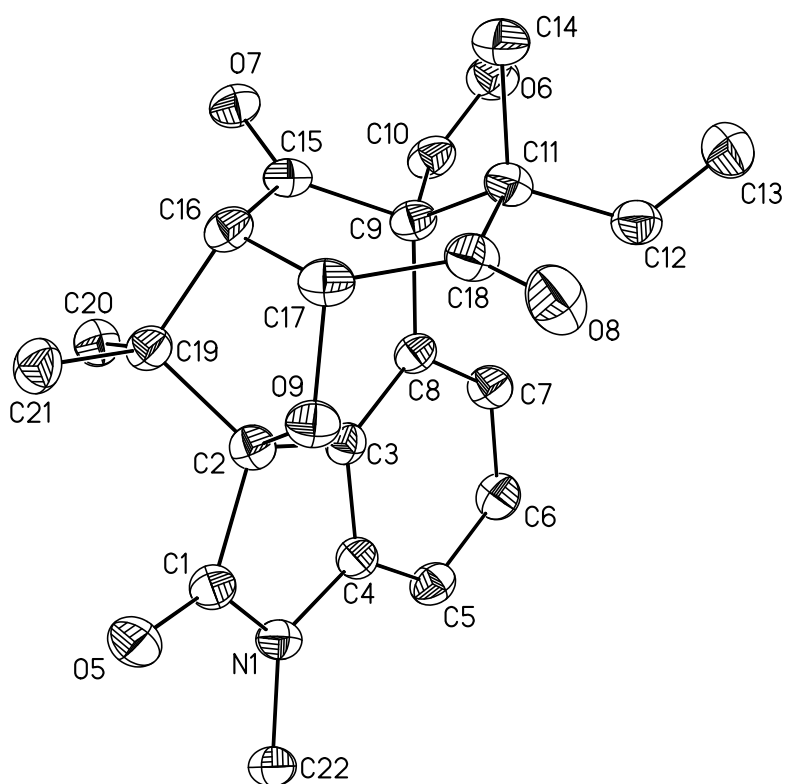
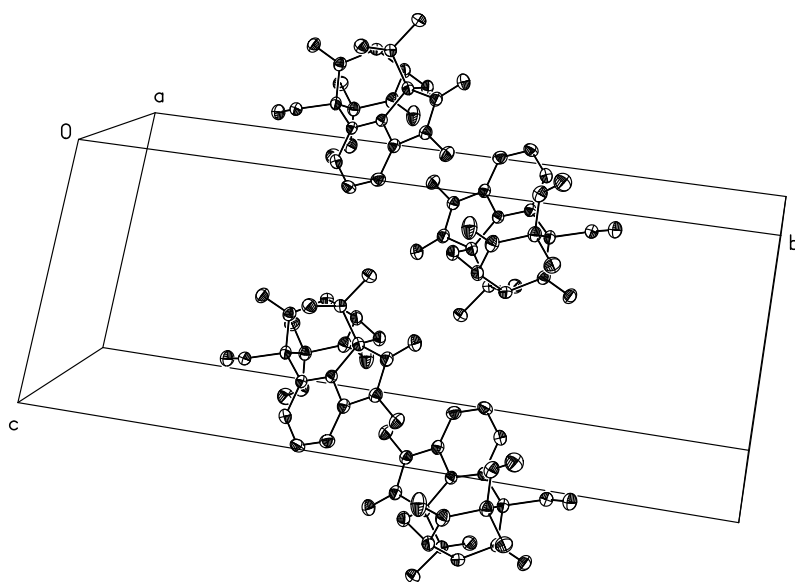
$$n = \text{number of independent reflections};$$

$$q, a, b, P \text{ as defined in [1]}$$

$$p = \text{number of parameters refined.}$$

### References

[1] All software and sources of scattering factors are contained in the SHELXTL (version 5.1) program library (G. Sheldrick, Bruker Analytical X-ray Systems, Madison, WI).



**Table S2.** Crystal and structure refinement for cyclic ether **17**.

Identification Code	Bhat06	
Empirical formula	C <sub>22</sub> H <sub>21</sub> NO <sub>5</sub>	
Formula weight	379.40	
Temperature	100 K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space Group	P2 <sub>1</sub> /c	
Unit cell dimensions	$a = 7.9092(15)$ Å	$\alpha = 90.0^\circ$
	$b = 25.245(5)$ Å	$\beta = 116.117(11)^\circ$
	$c = 9.7786(14)$ Å	$\gamma = 90.0^\circ$
Volume	1753.1(5) Å <sup>3</sup>	
Z	4	
Density (calculated)	1.437 Mg/m <sup>3</sup>	
Absorption coefficient	0.102 mm <sup>-1</sup>	
F(000)	800	
Crystal size, color, habit	0.24 x 0.24 x 0.20mm, transparent, irregular	
Theta range for data collection	1.61 – 28.35 °	
Index ranges	-10 ≤ h ≤ 10, -32 ≤ k ≤ 32, -13 ≤ l ≤ 13	
Reflections collected	16,580	
Independent reflections	4,272 (R <sub>int</sub> = 0.0267)	
Reflections with I > 4σ(F <sub>o</sub> )	2,918	
Absorption correction	SADABS based on redundant diffractions	
Max. and min. transmission	1.0, 0.787	
Refinement method	Full-matrix least squares on F <sup>2</sup>	
Weighting scheme	w = q [σ <sup>2</sup> (F <sub>o</sub> <sup>2</sup> ) + (aP) <sup>2</sup> + bP] <sup>-1</sup> where: P = (F <sub>o</sub> <sup>2</sup> + 2F <sub>c</sub> <sup>2</sup> )/3, a = 0.0635, b = 0.0, q = 1	
Data / restraints / parameters	4272 / 0 / 257	
Goodness-of-fit on F <sup>2</sup>	0.950	
Final R indices [I > 2 sigma(I)]	R1 = 0.0481, wR2 = 0.1138	
R indices (all data)	R1 = 0.0724, wR2 = 0.1213	
Largest diff. peak and hole	0.346, -0.187 eÅ <sup>-3</sup>	

**Table S3.** Atomic coordinates [ $\times 10^4$ ] and equivalent isotropic displacement parameters [ $\text{\AA}^2 \times 10^3$ ] for cyclic ether **17**.  $U(\text{eq})$  is defined as one third of the trace of the orthogonalized  $U_{ij}$  tensor.

	x	y	z	U (eq)	SOF
C (1)	7115 (2)	9874 (1)	7955 (2)	26 (1)	
C (2)	6108 (2)	9370 (1)	8116 (2)	23 (1)	
C (3)	5794 (2)	9055 (1)	6696 (2)	21 (1)	
C (4)	6487 (2)	9355 (1)	5858 (2)	24 (1)	
C (5)	6309 (2)	9207 (1)	4449 (2)	27 (1)	
C (6)	5384 (3)	8733 (1)	3862 (2)	28 (1)	
C (7)	4718 (3)	8423 (1)	4679 (2)	27 (1)	
C (8)	4899 (2)	8571 (1)	6114 (2)	22 (1)	
C (9)	4083 (3)	8196 (1)	6906 (2)	24 (1)	
C (10)	4392 (3)	7629 (1)	6515 (2)	28 (1)	
C (11)	1973 (2)	8337 (1)	6505 (2)	26 (1)	
C (12)	754 (3)	8315 (1)	4806 (2)	30 (1)	
C (13)	-612 (3)	7984 (1)	4067 (2)	39 (1)	
C (14)	1189 (3)	7994 (1)	7402 (2)	33 (1)	
C (15)	5190 (2)	8220 (1)	8641 (2)	25 (1)	
C (16)	5248 (2)	8731 (1)	9426 (2)	25 (1)	
C (17)	3584 (3)	9109 (1)	8532 (2)	27 (1)	
C (18)	1956 (3)	8903 (1)	7068 (2)	29 (1)	
C (19)	7020 (2)	9064 (1)	9623 (2)	25 (1)	
C (20)	8763 (3)	8746 (1)	9818 (2)	29 (1)	
C (21)	7521 (3)	9425 (1)	10999 (2)	31 (1)	
C (22)	8101 (3)	10232 (1)	6044 (2)	29 (1)	
N (1)	7298 (2)	9826 (1)	6637 (2)	25 (1)	
O (5)	7603 (2)	10251 (1)	8811 (2)	33 (1)	
O (6)	3272 (2)	7275 (1)	6146 (2)	35 (1)	
O (7)	6001 (2)	7828 (1)	9359 (1)	30 (1)	
O (8)	665 (2)	9198 (1)	6383 (2)	44 (1)	
O (9)	4354 (2)	9551 (1)	8051 (1)	26 (1)	

**Table S4.** Bond lengths [ $\text{\AA}$ ] and angles [ $^\circ$ ] for cyclic ether **17**.

C (1) -O (5)	1.212 (2)	C (9) -C (11)	1.577 (2)
C (1) -N (1)	1.364 (2)	C (10) -O (6)	1.196 (2)
C (1) -C (2)	1.545 (2)	C (11) -C (12)	1.510 (3)
C (2) -O (9)	1.435 (2)	C (11) -C (18)	1.535 (2)
C (2) -C (3)	1.523 (2)	C (11) -C (14)	1.543 (2)
C (2) -C (19)	1.535 (2)	C (12) -C (13)	1.304 (3)
C (3) -C (4)	1.393 (2)	C (15) -O (7)	1.219 (2)
C (3) -C (8)	1.400 (2)	C (15) -C (16)	1.492 (2)
C (4) -C (5)	1.373 (2)	C (16) -C (17)	1.547 (2)
C (4) -N (1)	1.405 (2)	C (16) -C (19)	1.571 (2)
C (5) -C (6)	1.388 (2)	C (17) -O (9)	1.445 (2)
C (6) -C (7)	1.378 (2)	C (17) -C (18)	1.534 (3)
C (7) -C (8)	1.397 (2)	C (18) -O (8)	1.201 (2)
C (8) -C (9)	1.535 (2)	C (19) -C (21)	1.527 (2)
C (9) -C (15)	1.530 (2)	C (19) -C (20)	1.533 (2)
C (9) -C (10)	1.531 (2)	C (22) -N (1)	1.455 (2)
O (5) -C (1) -N (1)	126.06 (16)	C (12) -C (11) -C (14)	112.53 (15)
O (5) -C (1) -C (2)	126.68 (16)	C (18) -C (11) -C (14)	104.47 (14)
N (1) -C (1) -C (2)	107.22 (14)	C (12) -C (11) -C (9)	111.03 (14)
O (9) -C (2) -C (3)	111.09 (14)	C (18) -C (11) -C (9)	107.17 (14)
O (9) -C (2) -C (19)	103.86 (13)	C (14) -C (11) -C (9)	112.21 (15)
C (3) -C (2) -C (19)	115.50 (13)	C (13) -C (12) -C (11)	127.22 (18)
O (9) -C (2) -C (1)	105.41 (13)	O (7) -C (15) -C (16)	121.09 (16)
C (3) -C (2) -C (1)	102.82 (13)	O (7) -C (15) -C (9)	120.44 (15)
C (19) -C (2) -C (1)	117.86 (15)	C (16) -C (15) -C (9)	118.47 (15)
C (4) -C (3) -C (8)	119.63 (15)	C (15) -C (16) -C (17)	114.63 (15)
C (4) -C (3) -C (2)	107.67 (14)	C (15) -C (16) -C (19)	110.48 (14)
C (8) -C (3) -C (2)	132.57 (15)	C (17) -C (16) -C (19)	103.28 (13)
C (5) -C (4) -C (3)	123.30 (16)	O (9) -C (17) -C (18)	104.96 (14)
C (5) -C (4) -N (1)	126.49 (16)	O (9) -C (17) -C (16)	106.57 (13)
C (3) -C (4) -N (1)	110.17 (15)	C (18) -C (17) -C (16)	118.32 (14)
C (4) -C (5) -C (6)	116.88 (16)	O (8) -C (18) -C (17)	117.98 (16)
C (7) -C (6) -C (5)	121.06 (16)	O (8) -C (18) -C (11)	121.10 (17)
C (6) -C (7) -C (8)	122.28 (16)	C (17) -C (18) -C (11)	120.92 (15)
C (7) -C (8) -C (3)	116.82 (15)	C (21) -C (19) -C (20)	109.42 (15)
C (7) -C (8) -C (9)	117.53 (15)	C (21) -C (19) -C (2)	112.02 (14)
C (3) -C (8) -C (9)	125.64 (15)	C (20) -C (19) -C (2)	113.63 (14)
C (15) -C (9) -C (10)	103.70 (14)	C (21) -C (19) -C (16)	107.40 (14)
C (15) -C (9) -C (8)	111.94 (14)	C (20) -C (19) -C (16)	116.10 (14)
C (10) -C (9) -C (8)	107.61 (14)	C (2) -C (19) -C (16)	97.78 (14)
C (15) -C (9) -C (11)	107.09 (13)	C (1) -N (1) -C (4)	112.05 (14)
C (10) -C (9) -C (11)	114.60 (15)	C (1) -N (1) -C (22)	124.02 (15)
C (8) -C (9) -C (11)	111.69 (14)	C (4) -N (1) -C (22)	123.75 (14)
O (6) -C (10) -C (9)	126.54 (18)	C (2) -O (9) -C (17)	106.10 (12)
C (12) -C (11) -C (18)	109.03 (15)		



**Table S5.** Anisotropic displacement parameters [ $\text{\AA}^2 \times 10^3$ ] for cyclic ether **17**. The anisotropic displacement factor exponent takes the form:  $-2\pi^2[h^2 a^{*2} U_{11} + \dots + 2hka^* b^* U_{12}]$

	$U_{11}$	$U_{22}$	$U_{33}$	$U_{23}$	$U_{13}$	$U_{12}$
C (1)	26 (1)	21 (1)	27 (1)	2 (1)	9 (1)	2 (1)
C (2)	26 (1)	20 (1)	25 (1)	-2 (1)	12 (1)	1 (1)
C (3)	22 (1)	20 (1)	21 (1)	1 (1)	8 (1)	3 (1)
C (4)	22 (1)	21 (1)	26 (1)	1 (1)	9 (1)	2 (1)
C (5)	29 (1)	30 (1)	26 (1)	4 (1)	15 (1)	2 (1)
C (6)	33 (1)	31 (1)	24 (1)	-3 (1)	15 (1)	1 (1)
C (7)	32 (1)	21 (1)	28 (1)	-3 (1)	14 (1)	1 (1)
C (8)	24 (1)	19 (1)	23 (1)	2 (1)	10 (1)	4 (1)
C (9)	28 (1)	17 (1)	26 (1)	1 (1)	13 (1)	2 (1)
C (10)	39 (1)	22 (1)	26 (1)	1 (1)	15 (1)	2 (1)
C (11)	26 (1)	22 (1)	30 (1)	0 (1)	13 (1)	-1 (1)
C (12)	30 (1)	26 (1)	34 (1)	4 (1)	15 (1)	0 (1)
C (13)	35 (1)	38 (1)	39 (1)	-3 (1)	13 (1)	-5 (1)
C (14)	36 (1)	33 (1)	35 (1)	3 (1)	20 (1)	-3 (1)
C (15)	27 (1)	22 (1)	29 (1)	4 (1)	15 (1)	-1 (1)
C (16)	32 (1)	24 (1)	22 (1)	2 (1)	14 (1)	2 (1)
C (17)	33 (1)	21 (1)	32 (1)	-1 (1)	18 (1)	1 (1)
C (18)	26 (1)	25 (1)	37 (1)	4 (1)	16 (1)	2 (1)
C (19)	30 (1)	21 (1)	22 (1)	0 (1)	12 (1)	1 (1)
C (20)	30 (1)	29 (1)	28 (1)	-1 (1)	12 (1)	-1 (1)
C (21)	38 (1)	29 (1)	23 (1)	-4 (1)	11 (1)	0 (1)
C (22)	29 (1)	24 (1)	32 (1)	5 (1)	12 (1)	-2 (1)
N (1)	28 (1)	21 (1)	27 (1)	2 (1)	12 (1)	-1 (1)
O (5)	40 (1)	23 (1)	34 (1)	-5 (1)	14 (1)	-4 (1)
O (6)	47 (1)	23 (1)	35 (1)	-1 (1)	17 (1)	-5 (1)
O (7)	34 (1)	24 (1)	32 (1)	6 (1)	14 (1)	3 (1)
O (8)	31 (1)	31 (1)	60 (1)	-3 (1)	11 (1)	5 (1)
O (9)	29 (1)	21 (1)	32 (1)	1 (1)	16 (1)	2 (1)

**Table S6.** Hydrogen coordinates [ $\times 10^4$ ] and isotropic displacement parameters [ $\text{\AA}^2 \times 10^3$ ] for cyclic ether **17**.

	x	y	z	U (eq)
H (5)	6795	9419	3902	33
H (6)	5208	8621	2881	34
H (7)	4115	8098	4252	32
H (10)	5594	7549	6570	34
H (12)	1011	8571	4211	35
H (13A)	-931	7720	4605	46
H (13B)	-1289	8008	2990	46
H (14A)	-134	8085	7090	50
H (14B)	1917	8061	8495	50
H (14C)	1286	7619	7190	50
H (16)	5305	8657	10450	30
H (17)	3064	9242	9233	32
H (20A)	8460	8527	8912	44
H (20B)	9156	8517	10716	44
H (20C)	9788	8990	9952	44
H (21A)	7969	9210	11927	46
H (21B)	6403	9625	10881	46
H (21C)	8513	9672	11072	46
H (22A)	8237	10562	6611	43
H (22B)	7267	10292	4964	43
H (22C)	9339	10117	6159	43

**Table S7.** Torsion angles [°] for cyclic ether **17**.

O(5)-C(1)-C(2)-O(9)	61.4(2)	C(10)-C(9)-C(15)-C(16)	178.17(15)
N(1)-C(1)-C(2)-O(9)	-116.48(15)	C(8)-C(9)-C(15)-C(16)	62.46(19)
O(5)-C(1)-C(2)-C(3)	177.85(17)	C(11)-C(9)-C(15)-C(16)	-60.27(18)
N(1)-C(1)-C(2)-C(3)	-0.02(18)	O(7)-C(15)-C(16)-C(17)	-156.12(16)
O(5)-C(1)-C(2)-C(19)	-53.9(2)	C(9)-C(15)-C(16)-C(17)	23.8(2)
N(1)-C(1)-C(2)-C(19)	128.27(16)	O(7)-C(15)-C(16)-C(19)	87.70(19)
O(9)-C(2)-C(3)-C(4)	110.73(15)	C(9)-C(15)-C(16)-C(19)	-92.34(18)
C(19)-C(2)-C(3)-C(4)	-131.34(16)	C(15)-C(16)-C(17)-O(9)	-110.43(15)
C(1)-C(2)-C(3)-C(4)	-1.59(18)	C(19)-C(16)-C(17)-O(9)	9.81(17)
O(9)-C(2)-C(3)-C(8)	-65.0(2)	C(15)-C(16)-C(17)-C(18)	7.4(2)
C(19)-C(2)-C(3)-C(8)	52.9(3)	C(19)-C(16)-C(17)-C(18)	127.61(15)
C(1)-C(2)-C(3)-C(8)	-177.32(18)	O(9)-C(17)-C(18)-O(8)	-61.7(2)
C(8)-C(3)-C(4)-C(5)	1.3(3)	C(16)-C(17)-C(18)-O(8)	179.67(16)
C(2)-C(3)-C(4)-C(5)	-175.05(16)	O(9)-C(17)-C(18)-C(11)	118.80(16)
C(8)-C(3)-C(4)-N(1)	179.05(15)	C(16)-C(17)-C(18)-C(11)	0.2(2)
C(2)-C(3)-C(4)-N(1)	2.66(19)	C(12)-C(11)-C(18)-O(8)	25.0(2)
C(3)-C(4)-C(5)-C(6)	0.1(3)	C(14)-C(11)-C(18)-O(8)	-95.5(2)
N(1)-C(4)-C(5)-C(6)	-177.27(16)	C(9)-C(11)-C(18)-O(8)	145.25(17)
C(4)-C(5)-C(6)-C(7)	-1.4(3)	C(12)-C(11)-C(18)-C(17)	-155.51(15)
C(5)-C(6)-C(7)-C(8)	1.3(3)	C(14)-C(11)-C(18)-C(17)	83.98(19)
C(6)-C(7)-C(8)-C(3)	0.1(3)	C(9)-C(11)-C(18)-C(17)	-35.3(2)
C(6)-C(7)-C(8)-C(9)	179.35(16)	O(9)-C(2)-C(19)-C(21)	-65.74(17)
C(4)-C(3)-C(8)-C(7)	-1.4(2)	C(3)-C(2)-C(19)-C(21)	172.38(14)
C(2)-C(3)-C(8)-C(7)	173.95(17)	C(1)-C(2)-C(19)-C(21)	50.4(2)
C(4)-C(3)-C(8)-C(9)	179.44(16)	O(9)-C(2)-C(19)-C(20)	169.63(14)
C(2)-C(3)-C(8)-C(9)	-5.2(3)	C(3)-C(2)-C(19)-C(20)	47.7(2)
C(7)-C(8)-C(9)-C(15)	149.23(16)	C(1)-C(2)-C(19)-C(20)	-74.27(19)
C(3)-C(8)-C(9)-C(15)	-31.6(2)	O(9)-C(2)-C(19)-C(16)	46.65(15)
C(7)-C(8)-C(9)-C(10)	35.9(2)	C(3)-C(2)-C(19)-C(16)	-75.23(16)
C(3)-C(8)-C(9)-C(10)	-144.90(17)	C(1)-C(2)-C(19)-C(16)	162.75(14)
C(7)-C(8)-C(9)-C(11)	-90.69(18)	C(15)-C(16)-C(19)-C(21)	-153.93(14)
C(3)-C(8)-C(9)-C(11)	88.5(2)	C(17)-C(16)-C(19)-C(21)	83.02(16)
C(15)-C(9)-C(10)-O(6)	105.5(2)	C(15)-C(16)-C(19)-C(20)	-31.1(2)
C(8)-C(9)-C(10)-O(6)	-135.79(19)	C(17)-C(16)-C(19)-C(20)	-154.20(14)
C(11)-C(9)-C(10)-O(6)	-10.9(3)	C(15)-C(16)-C(19)-C(2)	90.00(15)
C(15)-C(9)-C(11)-C(12)	-179.06(14)	C(17)-C(16)-C(19)-C(2)	-33.04(15)
C(10)-C(9)-C(11)-C(12)	-64.65(18)	O(5)-C(1)-N(1)-C(4)	-176.23(17)
C(8)-C(9)-C(11)-C(12)	58.05(18)	C(2)-C(1)-N(1)-C(4)	1.66(19)
C(15)-C(9)-C(11)-C(18)	61.96(17)	O(5)-C(1)-N(1)-C(22)	-0.9(3)
C(10)-C(9)-C(11)-C(18)	176.38(14)	C(2)-C(1)-N(1)-C(22)	177.01(15)
C(8)-C(9)-C(11)-C(18)	-60.92(18)	C(5)-C(4)-N(1)-C(1)	174.80(17)
C(15)-C(9)-C(11)-C(14)	-52.16(18)	C(3)-C(4)-N(1)-C(1)	-2.8(2)
C(10)-C(9)-C(11)-C(14)	62.25(19)	C(5)-C(4)-N(1)-C(22)	-0.6(3)
C(8)-C(9)-C(11)-C(14)	-175.05(14)	C(3)-C(4)-N(1)-C(22)	-178.18(15)
C(18)-C(11)-C(12)-C(13)	-127.9(2)	C(3)-C(2)-O(9)-C(17)	81.66(15)
C(14)-C(11)-C(12)-C(13)	-12.5(3)	C(19)-C(2)-O(9)-C(17)	-43.11(16)
C(9)-C(11)-C(12)-C(13)	114.2(2)	C(1)-C(2)-O(9)-C(17)	-167.67(13)
C(10)-C(9)-C(15)-O(7)	-1.9(2)	C(18)-C(17)-O(9)-C(2)	-106.27(14)
C(8)-C(9)-C(15)-O(7)	-117.59(17)	C(16)-C(17)-O(9)-C(2)	20.02(16)
C(11)-C(9)-C(15)-O(7)	119.68(17)		